Risk stratification Of Syncope in the Emergency department: The ROSE study

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Abstract

Background: To develop and validate a clinical decision rule to predict one-month serious outcome and all-cause death in patients presenting with syncope to a United Kingdom Emergency Department.

Methods: This was a single centre prospective observational derivation and validation cohort design study of patients aged 16 years or over presenting to a United Kingdom Emergency Department with syncope. A clinical decision rule was devised using a derivation cohort and then tested on a validation cohort.

Main Findings: Between 1st March and 27th October 2007, 550 patients were recruited into a derivation cohort. One-month serious outcome or all-cause death occurred in 40 (7.3%) patients and independent predictors were brain-type natriuretic peptide concentration ≥300 pg/mL (Odd Ratio=7.3), rectal examination showing faecal occult blood (OR=13.2), haemoglobin ≤90 g/L (OR=6.7), oxygen saturation ≤94% on room air (OR=3.0) and Q wave except in lead III on presenting electrocardiogram (OR=2.8). Chest pain and bradycardia ≤50 /min were also identified as predictors in the decision tree. Between 27th October 2007 and 22nd July 2008, 550 patients were recruited into a validation cohort. One-month serious outcome or all-cause death occurred in 39 (7.1%) patients. The ROSE rule had a sensitivity and specificity of 87.2% and 65.5% and a negative predictive value of 98.5%. For every 1,000 patients presenting with syncope, the ROSE rule would avoid 149 unnecessary admissions at the expense of missing 4 more patients with a potentially serious outcome compared to standard treatment, and no deaths. This is equivalent to 70,000 saved admissions per annum in the United Kingdom.

Other Findings: The Emergency Department management of syncope in the United Kingdom and Republic of Ireland is varied with only 18% of Emergency Departments having specific management guidelines. Acute myocardial infarction infrequently presents as syncope (1.4%) and can be diagnosed on presenting electrocardiogram. Troponin I may predict one-month serious outcome or all-cause death. Plasma D-dimer is commonly raised and consequently does not predict one-month serious outcome or death in syncope.

Interpretation: The ROSE rule has excellent sensitivity and negative predictive value and better specificity than existing rules and may be a valuable rule to help risk stratify patients presenting to the Emergency Department with syncope.

ii Declaration

This thesis is submitted to the University of Edinburgh for the degree of Doctor of Medicine. The work herein was composed by Dr Matthew Reed and carried out under the supervision of Dr Alasdair Gray, Consultant and Honorary Reader in Emergency Medicine, Department of Emergency Medicine, Edinburgh Royal Infirmary, Edinburgh, UK, and was undertaken within the Department of Emergency Medicine.

The work was carried out with the help of a research group, however their contributions are indicated and except where stated, this thesis is the result of my own work and in accordance with the University of Edinburgh regulations governing the degree of Doctor of Medicine. This thesis has not been submitted in whole or in part for any other degree or diploma at this or any other university.

_____ Date *26th July 2009*

During the period of research the following papers were published:

1. Reed MJ, Gray AJ. Collapse Query Cause - The Management of Adult Syncope in the Emergency Department *Emerg Med J* 2006; 23: 589-594.
2. Reed MJ, Newby DE, Coull AJ, Jacques KG, Prescott RJ, Gray AJ. The Risk stratification Of Syncope in the Emergency department (ROSE) pilot study: a comparison of existing syncope guidelines. *Emerg Med J* 2007; 24: 270-275.
3. Reed MJ, Newby DE, Coull AJ, Jacques KG, Prescott RJ, Gray AJ. Role of brain natriuretic peptide (BNP) in risk stratification of adult syncope. *Emerg Med J* 2007; 24: 769-773.

4. Bonney ME, Reed MJ, Gray AJ. The Prediction of Risk In Syncope using ECG characteristics (PRISE) pilot study: Can heart rate variability be used to predict risk in patients presenting to the emergency department with syncope? *Emerg Med J* 2009; 26: 32-36.
5. Stockley CJ, Bonney ME, Gray AJ, Reed MJ. Syncope Management in the UK and Republic of Ireland. *Emerg Med J* 2009; 26; 331-333.

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During the period of research the following abstract was published:

Reed MJ, Newby DE, Coull AJ, Jacques KG, Prescott RJ, Gray AJ. The Risk stratification Of Syncope in the Emergency department (ROSE) pilot study. *Emerg Med J* 2007; 24: 377 *(abstract 009)*

The following papers were accepted for publication:

1. Stockley CJ, Reed MJ, Newby DE, Coull AJ, Clegg GR, Gray AJ. The Utility of Routine D-dimer Measurement in Syncope. Accepted by *European Journal of Emergency Medicine* - 5th November 2008.
2. Reed MJ, Newby DE, Coull AJ, Prescott RJ, Gray AJ. Diagnostic and prognostic utility of troponin estimation in patients presenting with syncope. Accepted by *Emerg Med J* - 20th October 2008.
3. Reed MJ, Newby DE, Coull AJ, Jacques KG, Prescott RJ, Gray AJ. Risk stratification Of Syncope in the Emergency department: The ROSE study. *Emerg Med J* abstract.

The following papers were submitted for publication:

1. Reed MJ, Newby DE, Coull AJ, Jacques KG, Prescott RJ, Gray AJ. Risk stratification Of Syncope in the Emergency department: The ROSE study. Submitted to *The Journal of the American College of Cardiology* - December 2008.

2. Anderson CH, Reed MJ. The Influence of Temperature and Humidity on Emergency Department Syncope Attendances. Submitted to *European Journal of Emergency Medicine.*
3. Reed MJ. Management of syncope in the Emergency Department. Submitted to *Medica Minerva.*

During the period of research the following presentations were given at conferences:

1. The Risk stratification Of Syncope in the Emergency department (ROSE) pilot study. Oral presentation to College of Emergency Medicine Scientific Meeting; London, November 2006.
2. The ROSE study. Oral presentation to 'Trials in progress' session at College of Emergency Medicine Scientific Meeting; Sheffield, September 2007.
3. Near-patient BNP is able to predict three-month serious outcome in adult syncope patients presenting to the Emergency Department. Oral presentation to 4th Mediterranean Emergency Medicine Congress; Sorrento, Italy, September 2007.
4. The failure of D-dimer to predict risk in syncope. Moderated poster presentation to College of Emergency Medicine Autumn Scientific Meeting; Dublin, September 2008.
5. Syncope, the ED and the ROSE study. Presentation to the Futures of Academic Medics in Edinburgh; Edinburgh, September 2008.
6. Can heart rate variability predict risk and determine underlying cause in patients presenting to the emergency department with syncope? Presented by Martha Bonney to College of Emergency Medicine Autumn Scientific Meeting; Dublin, September 2008.
7. Reed MJ, Newby DE, Coull AJ, Jacques KG, Prescott RJ, Gray AJ. Risk stratification Of Syncope in the Emergency department: The ROSE study. Oral presentation to College of Emergency Medicine Spring Scientific Meeting; Brighton, April 2009.

During the period of research the following presentations were given at meetings:

1. The value of cardiac markers to rule out myocardial infarction in patients with syncope. Royal Society of Medicine A&E Section Meeting; London, September 2006.
2. Predicting serious outcome in patients with syncope. Royal Society of Medicine A&E Section Meeting; London, November 2007.

During the period of research the following poster presentations were made at conferences:

1. Prognostic and diagnostic utility of troponin estimation in patients presenting with syncope. College of Emergency Medicine Autumn Scientific Meeting; Dublin, September 2008.
2. The Risk stratification Of Syncope in the Emergency department (ROSE) pilot study: a comparison of existing guidelines. 4th Mediterranean Emergency Medicine Congress; Sorrento, Italy, September 2007.
3. Prognostic and diagnostic utility of troponin estimation in patients presenting with syncope. NHS Lothian Research Day, October 2008
4. The failure of D-dimer to predict risk in syncope. NHS Lothian Research Day, October 2008.
5. Stockley CJ, Bonney ME, Gray AJ, Reed MJ. Syncope Management in the UK and Republic of Ireland. Poster presentation to College of Emergency Medicine Spring Scientific Meeting; Brighton, April 2009.

iii Summary Table of Contents

Total thesis word count = 29418 words (excluding references and appendices)

Et al. has been used when there are more than three authors. If an author has more than one citation in any one year, the year has been referenced in the text. If there are many citations in any one year, each is referenced with the year followed by a, b, c, etc.

iv Detailed Table of Contents

v List of Tables and Figures

vi List of abbreviations

AAA	Abdominal Aortic Aneurysm
ACC	American College of Cardiology
ACEP	American College of Emergency Physicians
ACP	American College of Physicians
AF	Atrial Fibrillation
AMI	Acute Myocardial Infarction
AV	Atrio-Ventricular
β-hCG	β-subunit of human Chorionic Gonadotrophin
BNP	Brain-type Natriuretic Peptide
BTS	British Thoracic Society
CCF	Congestive Cardiac Failure
CDR	Clinical Decision Rule
CHB	Complete Heart Block
CRP	C-Reactive Protein
CT	Computed Tomography
CTPA	Computed Tomography Pulmonary Angiogram
DCF	Data Collection Form
ECG	Electrocardiogram
ED	Emergency Department
EEG	Electroencephalogram
EPR	Electronic Patient Record
ESC	European Society of Cardiology
FBC	Full Blood Count
GI	Gastrointestinal
GP	General Practitioner
GTN	Glyceryl Tri-Nitrate
Hb	Haemoglobin
HS-CRP	High Sensitivity C-Reactive Protein
LP	Lumbar Puncture
LR	Likelihood Ratio
MI	Myocardial Infarction
MOPD	Medical Outpatients Department
OESIL	Osservatorio Epidemiologico sulla Sincope nel Lazio
PE	Pulmonary Embolism
PR	Per Rectum (rectal) examination
PVC	Premature Ventricular Complex
ROC	Receiver Operator Characteristic
RIE	Royal Infirmary of Edinburgh
SAH	Subarachnoid Haemorrhage
SFSR	San Francisco Syncope Rule
ROSE	Risk stratification Of Syncope in the ED
UK	United Kingdom
US	United States
VF	Ventricular Fibrillation
VQ	Ventilation Perfusion
VT	Ventricular Tachycardia

vii Dedication

This thesis is dedicated to my family: my parents for their encouragement and drive and most importantly my wife Susan, for her love, support and willingness to take on all household chores during the many months that it took me to finally complete this work.

viii Acknowledgements

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Chapter 1

Introduction, Background and Literature review

1.1 Introduction

Syncope is a transient loss of consciousness with an inability to maintain postural tone followed by spontaneous recovery (Morag R). The word derives from a Greek term meaning 'to cut short' and may have been first described by Hippocrates (Maisel WH et al). Syncope accounts for approximately three percent of ED visits and between one and six percent of acute hospital medical admissions affecting six per 1,000 people per year (Maisel WH et al, Soteriades ES et al).

Clinical assessment of syncope is challenging due to the many and varied underlying causes which range from benign vasovagal (or neurocardiogenic) syncope, to potentially fatal arrhythmias and PE. There is evidence that syncope patients are not well managed in the UK; Thakore et al in 1999 looked at practice in one UK ED and showed that few patients had relevant syncope symptoms documented and 25% did not have an ECG recorded. Also, 28% with an abnormal ECG and 40% with a history of organic heart disease were sent home from the ED.

In this first chapter, the background to this thesis will be discussed. Current management of adult ED syncope patients and the available evidence will be explored.

1.2 Literature Search

The information in this background section was obtained from a literature review using the search strategy detailed in Figure 1.1. The search was performed at the beginning of the study and then repeated again just prior to initial submission. During the period of the study an electronic mail alert was set up using MEDLINE and the search strategy in Figure 1.1 in order to review all potentially relevant studies published during the course of the research.

Figure 1.1 Search Strategy

1	SYNCOPE, VASOVAGAL/ or SYNCOPE/ or syncope.mp.
2	Emergency Service, Hospital/ or emergency department.mp. or Emergency Medical Services/
3	1 and 2

The search was applied via the OVID interface, to MEDLINE (1966 to 2008 week 48), EMBASE (1980 to 2008 week 48) and the Cochrane Database of Systematic Reviews.

Inclusion criteria: All articles that were relevant to the management of adult syncope patients in the ED were included.

Exclusion criteria: Non-human studies were excluded. No other limits were placed on the search.

The abstracts of all papers identified were read to determine relevance. The full texts of relevant articles were then obtained and read to determine if they should be included in the review. The references of all papers designated for review inclusion were also hand-searched to identify further suitable studies.

1.3 Diagnosis of syncope

In the 1980's, the commonest underlying diagnosis of syncope was neurocardiogenic syncope (37 to 40%). Other diagnoses included arrhythmia (8 to 20%), orthostatic hypotension (8 to 10%), situational syncope (3 to 8%), organic heart disease (4 to 8%) and carotid sinus syncope (1%) (Dunn MJG et al, Martin GJ et al, Lipitz LA et al 1985, Silverstein MD et al, Krol RB et al, Denes P et al, Middlekauff H et al). In

31 to 47 per cent of patients no cause of syncope is found (Dunn MJG et al, Martin GJ et al, Lipitz LA et al 1985, Silverstein MD et al, Krol RB et al, Denes P et al, Middlekauff H et al). With increased availability of tilt testing, 24-hour tape monitoring and loop recording, an underlying cause is now more likely to be ilicited. Commonly this is not apparent during initial ED assessment (Sarasin FP et al 2001).

Brignole et al rigidly applied the ESC guidelines (Brignole et al 2001, Brignole et al 2004) to 541 patients across 11 Italian general hospitals and found a definite cause of syncope in 98% with the initial evaluation establishing a diagnosis in 50% (Brignole M et al 2006b). The most recent study employing diagnostic algorithms and newer diagnostic modalities suggests that unexplained syncope still accounts for 14% of all patients (Sarasin FP et al 2001) [Figure 1.2].

1.4 Usefulness of history

A history of transient loss of consciousness followed by spontaneous recovery must be elicited. A thorough history and physical examination may determine the reason for syncope in approximately 40% of patients (Day SC et al, Kapoor W 1990, Oh JH et al, Martin TP et al). Most patients do not remember their syncopal episode. Some patients can recall the event as it may terminate just prior to the loss of consciousness ('pre-syncope').

It is important to identify features in the history that may point to seizure activity, the most important of which is the presence of a post-ictal phase. While confusion may be present immediately after syncope, this should be brief (Morag R). Other discriminators such as tonic-clonic activity, incontinence and tongue biting may help, however do not in isolation rule out syncope if a period of cerebral anoxia has occurred (Dunn MJG et al). Seizure activity may occur due to a period of cerebral anoxia.

The presence of pre-syncopal symptoms such as nausea, diaphoresis, dizziness and a feeling of warmth may suggest neurocardiogenic syncope (Oh JH et al, Martin GL et al, Calkins H et al). Precipitant factors e.g. micturition and coughing may suggest situational syncope, and a positional aspect i.e. syncope precipitated by rising from a

sitting position, may suggest orthostatic syncope. Kapoor et al found that neurocardiogenic syncope, orthostatic hypotension and situational syncope were the diagnoses most commonly made on the basis of history and examination alone, and accounted for 30% of syncope presentations (Kapoor W 1990).

Figure 1.2 Diagnosis of cause of syncope in 650 patients (Sarasin FP et al).

Cause of Syncope	Number	Percentage
Non-cardiac causes	**456**	**70**
Vasodepressor syncope	242	37
Orthostatic hypotension	158	24
Neurological	30	5
Psychiatric	11	2
Other	9	1.5
Carotid sinus hypersensitivity	6	1
Unknown	**92**	**14**
Cardiac	**69**	**11**
Arrhythmias	44	7
Sinus Bradycardia or pause	15	2
Atrioventricular block	15	2
Ventricular tachycardia	9	1.5
Supraventricular tachycardia	4	0.5
Pacemaker malfunction	1	0.2
Acute coronary syndrome	9	1.5
Aortic stenosis	8	1
PE	8	1
Incompletely assessed	**33**	**5**

Other important symptoms prior to the syncopal event include chest pain, sudden onset of headache or dyspnoea, palpitations, back pain or focal neurological deficits. The presence of any of these may suggest an alternative serious cause. A brief or absent pre-syncopal period may be associated with syncope of a cardiac nature, especially an arrhythmia (Calkins H et al). Here, an average length of pre-syncopal symptoms of three seconds has been reported (Martin GJ et al). Syncope associated with neurocardiogenic syncope has been reported to last an average of two and a half minutes (Morag R, Martin GJ et al). Recurrent episodes of syncope, whilst leading

to an increased likelihood of injury, are not associated with major morbidity. Mortality decreases with increasing syncope frequency (Kapoor et al 1987, Kapoor 1990). Calkins et al found that patients suffering syncope secondary to arrhythmias were more likely to be male, aged over 54, to have less than five seconds of pre-syncope warning, and less likely to have had previous syncope episodes, compared to those patients with neurocardiogenic syncope. This latter group were more likely to have palpitations, blurred vision, and feelings of nausea, warmth and light-headedness prior to the syncope episode, and feelings of nausea, warmth, dizziness and fatigue afterwards (Calkins et al).

A witness history should be sought and a drug history taken to identify the use of antihypertensive or other cardiac medication, and drugs that cause bradycardia, hypotension or prolong the QT interval (e.g. erythromycin, quinine and major tranquilizers). Nitrate use immediately prior to the syncopal episode is associated with GTN syncope. A menstrual history should also be taken in women of childbearing age as syncope is not an uncommon presentation of ectopic pregnancy. In addition neurocardiogenic syncope is relatively common in early pregnancy.

Some patients presenting with syncope may be under the influence of alcohol or recreational drugs making a thorough history difficult. Whilst these substances may lead to collapse, syncope is unlikely to occur as a direct consequence of either alcohol or recreational drugs. These patients should be assessed at the time of presentation with a thorough examination and ECG, however subsequent assessment of risk and additional investigations may need to wait until the patient is more compliant.

Finally, a family history of cardiac disease or sudden unexplained family death or history of syncope precipitated by exercise raise the possibility of hypertrophic cardiomyopathy, Brugada's syndrome or pre-excitation disorders such as congenital long QT syndrome and arrhythmogenic right ventricular dysplasia, which can be precipitated by a sympathetic surge.

1.5 Examination findings

A detailed physical examination should be performed, vital signs obtained and a point of care blood glucose measured. The cardiovascular system should be specifically examined looking for a postural drop (a fall of 20mmHg or more, or a fall to <90mmHg after standing for at least three minutes), a displaced cardiac apex beat, valve lesions, the presence of cardiac failure, carotid bruits and a ventricular pause of greater than three seconds precipitated by carotid sinus massage (Morag R).

This final test is diagnostic for carotid sinus hypersensitivity and should be performed if syncope may have been precipitated by neck movements or pressure on the neck. It is important to first exclude the presence of a carotid bruit and to be aware of the risk of precipitating a prolonged sinus pause or an episode of hypotension. Firm, longitudinal massage should be performed over the site of maximal pulsation of the right carotid sinus, located between the superior border of the thyroid cartilage and the angle of the mandible for a minimum of five and a maximum of ten seconds (Parry SW & Kenny RA). The procedure is considered positive if associated with an episode of asystole longer than three seconds and/or a fall in systolic blood pressure of 50 mmHg or more during or immediately after the massage. If non-diagnostic the procedure should be repeated in the left supine, and right and left 70° head-up position. Patients should also have intravenous access and be in an area where resuscitation equipment is available if required. Neurological examination should attempt to identify signs suggestive of seizure activity pointing towards a primary neurological seizure rather than true syncope. Finally, evidence of related trauma should be sought and a rectal examination performed to identify gastrointestinal haemorrhage if suggested by the history.

Oh et al prospectively studied 497 syncope patients to determine whether symptoms and co-morbidities predicted adverse outcome. History and physical examination identified a cause in 222 (47%) patients. In the remaining patients, the absence of pre-syncopal nausea and vomiting (odds ratio 7.1) and the presence of ECG abnormalities (odds ratio 23.5) were predictors of arrhythmic syncope.

1.6 Use of investigations

Despite FBC and urea and electrolyte estimation seeming reasonable investigations in syncope, except for a profoundly low haematocrit (Quinn et al 2004) laboratory investigations have not been shown to discriminate in the management of syncope (Martin GJ et al, Lipitz LA et al, Junaid A et al) and current guidelines do not recommend routine testing (Brignole et al 2001, Brignole et al 2004).

In one study of syncopal patients, two of 134 patients were found to be hypoglycaemic (Martin GJ et al), and one later diagnosed with diuretic induced orthostatic hypotension was hyponatremic (Martin TP et al). Four in 134 patients with syncope secondary to gastrointestinal haemorrhage had an abnormal haematocrit that dropped with rehydration (Morag R), however on each occasion the diagnosis was suspected on clinical grounds. A urine β-HCG should be considered in all women of childbearing age to rule out an ectopic pregnancy.

The only studies that have shown brain CT and EEG to be helpful have included primary neurological seizures as a cause of syncope. All other studies have shown no benefit in performing these or any radiological investigations in the management of syncope (Kapoor W 1990, Martin GJ et al, Silverstein MD et al, Kapoor et al 1983, Eagle K and Black H).

1.7 Electrocardiogram

A standard 12-lead ECG is warranted in all cases of syncope unless the history and physical examination reveal an obvious non-cardiac cause. This initial ECG is normal in most patients with syncope (Day SC et al, Kapoor WN 1990, Martin GJ et al, Kapoor WN et al 1983, Eagle K and Black H, Kapoor WN et Hanasu BH 1996). Martin GJ et al suggested that the ECG is diagnostic in only two percent of patients whilst Kapoor 1990 found that 28 out of 433 patients (6%) had a diagnostic initial ECG. Martin GJ et al also found that the presence of an abnormal ECG (defined as any abnormality of rhythm or conduction, ventricular hypertrophy, or evidence of prior myocardial infarction, but excluding non-specific ST-segment and T-wave changes) was a multivariate predictor for arrhythmia or death within one year of

syncope (Martin TP et al). A further study showed that an abnormal ECG, defined as rhythm or conduction abnormality, AV block, signs of an old MI, left or right ventricular hypertrophy or frequent PVCs was a predictor for arrhythmic syncope (Oh JH et al). Equally a normal ECG is associated with negative electrophysiology studies (Kapoor WN 1990), and a low risk for syncope secondary to a cardiovascular cause (Martin TP et al, Brignole M et al 2004, Krol RB et al, Denes P et al). The ECG also allows assessment of the QT interval and may suggest disorders such as Wolff-Parkinson-White syndrome (Klitzner TS).

The current ESC syncope guidelines (Brignole M et al 2004) document the ECG abnormalities that increase the risk of a syncope secondary to arrhythmia: Bifascicular block, QRS >0.12 seconds, Mobitz second degree AV block, sinus bradycardia (< 50 bpm), sinoatrial block, sinus pause > three seconds, pre-excited QRS complexes, prolonged QT interval, signs of Brugada syndrome (right bundle branch block, ST segment elevation in leads V1 to V3) or arrhythmogenic right ventricular dysplasia (epsilon wave or localised QRS >110 msecs in V1-V3, or inverted T waves in V2 and V3 without right bundle branch block), and Q-waves suggesting AMI. It is suggested that patients with these abnormalities should be admitted for monitoring and be investigated for arrhythmic syncope. There is no evidence that any of these findings are associated with an early adverse outcome and no studies have been powered to assess the prognostic value of ECG abnormalities.

1.8 Other cardiac investigations

For patients considered at risk of having an arrhythmic cause for their syncope, longer ECG assessment in the form of 24-hour tape monitoring and loop recording may be considered on either an inpatient or outpatient basis. These investigations have good sensitivity however patients suffering arrhythmias may not demonstrate abnormalities during the monitoring period. Whilst arrhythmias demonstrated during routine ED monitoring are obviously diagnostic, more prolonged monitoring does not form part of ED investigation. Echocardiography is also considered part of syncope investigation. There is no evidence yet that ED echocardiography is able to aid early risk stratification, however may prove helpful in the future.

1.9 Cardiac markers

The routine measurement of cardiac markers in adult patients presenting to the ED with syncope has a diagnostic yield for AMI of less than 1% (Link MS et al, Grossman SA et al, Hing R et al). This may be higher in elderly patients who are more likely to present with atypical symptoms of AMI such as syncope (Bayer et al). Even in this group, the number of patients who do not have other features suggestive of AMI is small (Link MS et al). Other groups prone to 'silent' AMI such as diabetics have not been investigated. There is no evidence that raised cardiac markers have any prognostic value (Hing R et al, Lipsitz LA et al 1987).

1.10 Brain-type natriuretic peptide

BNP, which is secreted in response to an increase in ventricular volume and pressure load, is known to be an excellent marker of prognosis in patients with heart failure or cardiac disease (Doust JA et 2004, Doust et al 2005). It is well established that prognosis in syncope is related to the presence of underlying heart disease (Kapoor WN et al 1996), and all existing syncope CDRs include either a history of CCF (Martin GJ et al, Oh JH et al, Colivicchi F et al, Sarasin FP et al 2003, Quinn JV et al 2004, Quinn JV et al 2006) or of underlying cardiac disease (Martin GJ et al, Oh JH et al). Tanimoto et al in 2004 conducted the only syncope study to date that has utilised BNP (Tanimoto et al). This study evaluated the usefulness of BNP to separate cardiac and non-cardiac causes of syncope. The investigators retrospectively evaluated 148 consecutive syncope patients admitted to hospital. 61 of these patients were found to have a cardiac cause for their syncope. BNP ≥40 pg/ml was 82% sensitive and 92% specific for identifying cardiac syncope.

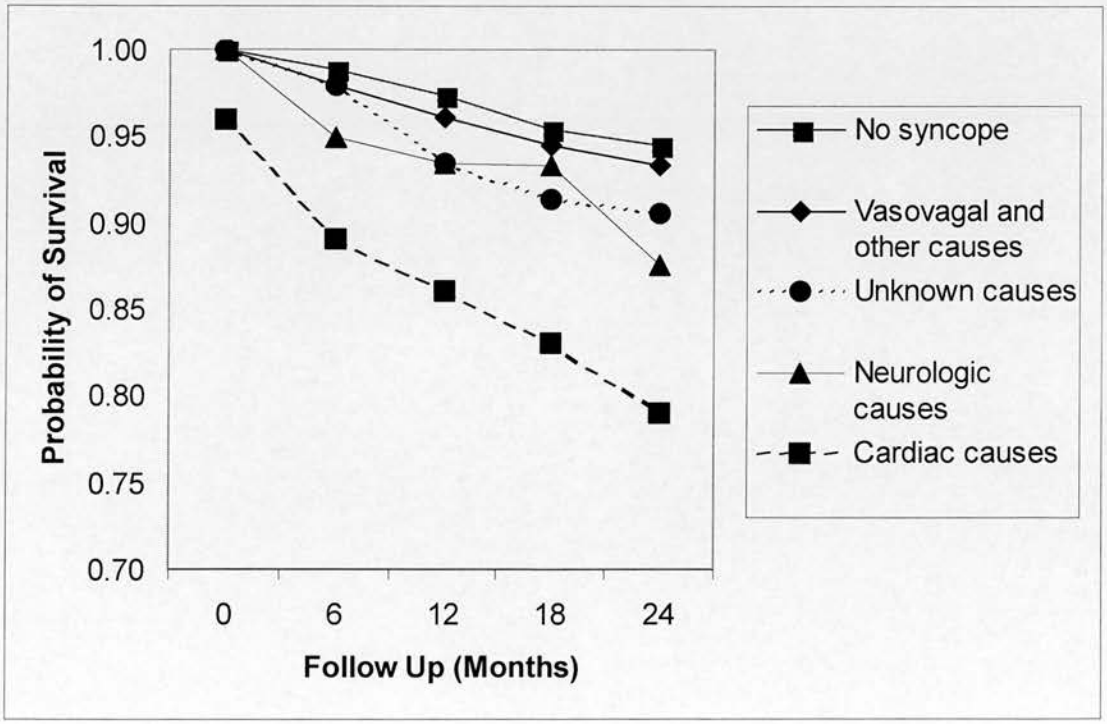
1.11 Stratification by cause of syncope

Kapoor et al 1983, published the first prospective study of 204 syncopal patients. A cardiovascular cause (i.e. arrhythmia, aortic stenosis, AMI, PE, dissecting aortic aneurysm) was determined in 53 patients, a non-cardiovascular cause in 54, and in 97 patients no cause was identified. At 12 months, mortality was 14%. Mortality was greatest in the patients in whom a cardiovascular cause had been identified (30%)

compared to the patients in whom a non-cardiovascular cause had been identified (12%), and in those in whom no cause had been found (6.4%). Sudden death (defined as death within 24 hours of the onset of symptoms) was found to be greater in the patients in whom a cardiovascular cause had been identified (24%) compared with a non-cardiovascular cause (4%) and an unknown cause (3%). This study was the first to highlight the greater risk to a patient whose syncope is due to a cardiac cause.

Soteriades ES et al studied 7,814 participants of the Framingham heart study. 822 (6.2 per 1,000 person years) had syncope in the 17 years of follow up. Neurocardiogenic syncope, the most common cause (21.2%), was not associated with any increased risk of death however a cardiac cause for syncope, found in 9.5%, was associated with a two-fold increase in death, and a six-month mortality rate exceeding 10% [Figure 1.3].

Figure 1.3 Overall survival of participants with syncope according to cause, and participants without syncope, amongst 7,814 participants of the Framingham heart study.



Getchell WS et al studied elderly hospitalised patients (mean age 73) presenting with syncope and showed that mortality was not associated with a cardiac cause for syncope, but rather with age and co-morbid illnesses (Getchell WS et al).

Subsequent studies controlling for cardiac mortality have showed that the higher mortality in patients with syncope due to a cardiovascular cause is largely related to underlying cardiovascular disease (Oh JH et al, Kapoor WN et al 1983, Middlekauff H et al). A study comparing patients with and without syncope, who were matched for cardiac disease showed that syncope itself was not a significant predictor of one-year survival (Kapoor WN and Hanasu 1996), however male gender, age over 55 years and CCF were. Middlekauff H et al in 1993 studied 491 patients with advanced cardiac failure, 60 of who had an episode of syncope. One-year mortality was greater in the cardiac failure patients who had a history of syncope, compared to a matched group of cardiac failure patients without a syncope history (45% versus 12%). The major predictor of sudden death however was poor left ventricular function, not whether the cause of the syncope was cardiac or not (Middlekauff H et al). This study demonstrated syncope itself to be a good predictor of mortality. Whether these results are applicable to other patient populations is unclear.

It therefore seems it is the presence of significant underlying heart disease that is associated with a poor prognosis in syncope. It is likely that the presence of cardiac failure, commonly secondary to coronary artery disease, predisposes the patient to arrhythmias and consequent syncope or sudden death. Syncope patients with signs of cardiac failure should be considered high risk and therefore investigated to delineate underlying heart disease and the cause of syncope, in an attempt to reduce mortality (Kapoor WN and Hanasu BH 1996, Kapoor WN 2002).

1.12 Clinical decision rules

Clinical experience provides clinicians with an intuitive sense of which findings on history, physical examination, and investigation are important in assessing a patient's fate. A CDR is a clinical tool that quantifies the individual contributions that various components of the history, physical examination, and basic laboratory results make

toward the diagnosis, prognosis, or likely response to treatment in a patient. CDRs attempt to formally test, simplify, and increase the accuracy of clinicians' diagnostic and prognostic assessments (McGinn TG et al 2000).

To date, there have been seven syncope risk stratification studies (Martin GJ et al, Oh JH et al, Colivicchi F et al, Sarasin FP et al 2003, Quinn JV et al 2004 and Quinn JV et al 2006, Costantino et al, Del Rosso et al). Some of these have involved small numbers of patients (n=252 & 374; Martin GJ et al, n=270 & 328; Colivicchi F et al, n=175 & 269; Sarasin FP et al 2003, n=260 & 256; Del Rosso et al), some have not been validated (Oh JH et al) and all have used different predictor variables. Only two studies (Quinn JV et al 2004, Quinn JV et al 2006, Costantino et al) have looked at short-term adverse outcomes, relevant to emergency practice.

Martin et al prospectively developed and validated a risk stratification system for patients presenting to the ED with syncope (Martin TP et al). 252 patients were enrolled into a derivation cohort and 374 into a validation group. Four factors were predictive of one-year mortality or arrhythmia occurrence [Figure 1.4]. One-year mortality and arrhythmia risk in patients with none of the four risk factors was between 4.4 and 7.3%. This increased to between 57.6 and 80.4% in patients with three risk factors.

In patients without an obvious diagnosis in the ED, emphasis subsequently moved to risk stratification into groups correlating with mortality and to focus resources into monitoring and investigating high-risk patients in an effort to reduce mortality. Oh et al found that history and physical examination was able to determine a cause in 47% of patients. The only independent predictor of one-year mortality was the presence of underlying cardiac disease (defined as coronary artery disease, valvular disease, cardiomyopathy, CCF or other organic heart disease found clinically or during investigations). Crane SD conducted the only UK ED study of syncope outcome. This retrospective study of 210 patients presenting during an eight week period showed that it is possible to stratify UK ED syncope patients according to ACP guidelines (Linzer M et al 1997a, Linzer M et al 1997b).

Figure 1.4 Martin GJ et al

Martin GJ et al

Four factors were predictive of one-year mortality or arrhythmia occurrence.

1 Abnormal presenting ECG
- rhythm abnormalities
- frequent PVCs
- conduction disorders
- left or right ventricular hypertrophy
- short PR interval
- evidence of an old MI
- AV block

2 A history of ventricular arrhythmias

3 A history of CCF

4 Age greater than 45 years.

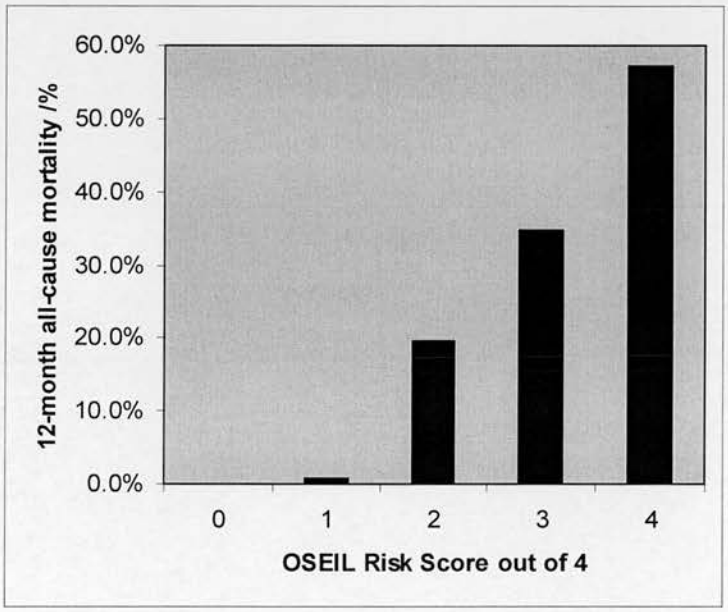
Patients in ACP group one (high risk), had a one-year mortality of 36%, compared to patients assigned to ACP group two (intermediate risk) (14%), and ACP group three (low risk) (0%). Shen WK et al showed that patients in an intermediate risk group can be investigated in an ED based syncope unit leading to an increased diagnostic yield, reduced hospital admission and total length of hospital stay without affecting recurrent syncope and mortality (SEEDS study; Shen WK).

Colivicchi F et al performed a six-centre study that recruited 270 patients into a derivation study and 328 into a validation group. They developed a risk score (OESIL score) based on four characteristics [Figure 1.5]. The authors found that one-year mortality increased with increasing risk score and suggested that the tool could therefore be used in the assessment of ED syncope patients [Figure 1.6].

Figure 1.5 The OESIL score (Colivicchi F et al)

OESIL score	
1	Age >65
2	History of cardiovascular disease
3	Syncope without prodromal symptoms
4	An abnormal ECG (rhythm abnormalities, AV or intraventricular conduction disorders, left or right ventricular hypertrophy, left axis deviation, old MI, ST segment or T wave abnormalities).
The presence of each characteristic scores one.	
No admission cut off defined.	

Figure 1.6 Rates of 12-month all-cause mortality according to the OESIL score in the OESIL derivation cohort.



Sarasin FP et al prospectively recruited 175 Swiss patients with unexplained syncope after ED investigation into a derivation study, and 269 similar US patients into a validation group. They found that predictors for arrhythmic syncope were abnormal ECG, a history of CCF, and age over 65. Risk of arrhythmia (diagnosed by 24-hour Holter or loop recorder abnormalities) rose from between 0 and 2% in patients with

no risk factors, to 6-17% in patients with one risk factor, 35-41% in those with two, and 27-60% in those with all three risk factors. They concluded that a risk score based on clinical and ECG factors is able to identify patients in the ED at risk of arrhythmia. Del Rosso et al derived and validated a score from clinical history to predict cardiac syncope. They assigned a score from +4 to -1 to the following factors which were found to be predictors: abnormal ECG and/or heart disease, palpitations before syncope, syncope during effort or in supine position, absence of autonomic prodromes and absence of predisposing and/or precipitating factors. A score ≥ 3 identified cardiac syncope with a sensitivity of 95%/92% and a specificity of 61%/69% in the derivation and validation cohorts, respectively.

Few studies have directly evaluated the short-term risk of syncope (Brignole M et al 2008). The most recent and largest derivation study on syncope risk stratification was performed by Quinn JV et al (Quinn JV et al 2004, Quinn JV et al 2006). They prospectively studied 684 patients who presented to a US ED with syncope, 79 of whom experienced a serious seven-day outcome. 26 of the 50 studied predictor variables were associated with a serious outcome. A CDR (SFSR) was devised using five risk factors [Figure 1.7]. This rule was found to be 96% sensitive and 62% specific at predicting serious short-term outcome and if applied to the derivation cohort, would have decreased hospital admissions by 10%.

Figure 1.7 The San Francisco Syncope Rule
(Quinn JV et al 2004, Quinn JV et al 2006)

The San Francisco Syncope Rule

1 Abnormal ECG (not sinus/new changes compared to previous ECG)
2 Haematocrit <30%
3 A complaint of shortness of breath
4 Initial systolic blood pressure <90 mmHg
5 History of CCF .

Presence of <u>any</u> characteristic warrants admission.

In this study, two of the risk markers included in the rule would usually necessitate immediate hospital admission: systolic blood pressure <90 mmHg and haematocrit <30%. The researchers also derived their rule using seven-day outcome but attempted to validate it using one-month outcome (Quinn et al 2006). Despite promising results in their validation study, subsequent attempts to externally validate it have failed (Fischer CM et al, Stracner DL et al, Sun BC et al, Schladenhaufen R et al). Sensitivity and specificity in these studies was much lower than in the Quinn et al 2006 validation cohort (sensitivity = 52%, 91% and 89%, specificity = 84%, 54% and 42%; Fischer CM et al, Stracner DL et al, Sun BC et al), in one study missing 26 of the 50 patients who had a serious outcome (Fischer CM et al). An attempt has also been made to validate the rule for long-term (one-year) mortality with a sensitivity of 88% and specificity of 56% in 658 ED attendees (Quinn JV et al 2005).

A recent study by Costantino et al, aimed to compare risk factors associated with short-term (10 days) and long-term (one year) syncope prognosis in 676 subjects presenting to the ED with syncope who did not have a condition likely to require hospital admission. Forty-one subjects (6.1%) experienced severe outcomes including five deaths (0.7%) in the 10 days after presentation. Figure 1.8 details factors associated with poor short-term outcome.

Figure 1.8 STePS study (Costantino G et al)

STePS short-term syncope risk factors:	
1	An abnormal ECG (AF/tachycardia, sinus pause >2 s, sinus bradycardia, conduction disorders (bundle branch block, second-degree Mobitz I AV block), signs of previous MI or ventricular hypertrophy or multiple PVCs)
2	Concomitant trauma
3	Absence of symptoms of impending syncope
4	Male gender

Long-term poor outcomes occurred in 9.3% and included 40 deaths (6.0%). Long-term poor outcome was correlated with age > 65 years and a history of neoplasm, cerebrovascular disease, structural heart disease and ventricular arrhythmia.

With underlying cardiac failure being associated with a poor prognosis in syncope, CDRs utilising biochemical markers of cardiac failure severity (e.g. CRP or BNP) (Doust et al 2004, Doust et al 2005, Tanimoto K et al, Alonso-Martinez JL et al) may prove useful in the future. As yet these have not been studied in the context of syncope.

1.13 Guidelines

The 1997 ACP guidelines (Linzer M et al 1997a, Linzer M et al 1997b) reviewed all existing literature in order to provide guidelines on diagnosing syncope. They included guidance on which patients with unexplained syncope should be admitted to hospital, and divided patients into groups depending on the apparent risk of adverse outcome. Three main groups were identified. High risk patients in whom admission was indicated were those with a history of coronary artery disease, CCF or VT, those with accompanying symptoms of chest pain, those with physical signs of CCF, significant valve disease, stroke or focal neurology, and patients with ECG findings of ischemia, arrhythmia (serious bradycardia or tachycardia), long QT interval or bundle branch block. The second group identified were those in whom they felt admission was often indicated. This 'intermediate risk' group included patients with a sudden loss of consciousness with injury, tachycardia or exertional syncope, those with frequent episodes (which lead to an increased likelihood of injury but are not associated with an increased mortality), those with a suspicion of coronary heart disease or arrhythmia, moderate to severe postural hypotension, and those aged over 70 years. A third 'low risk' group was defined as those who do not fall into either of the above groups. These patients may be discharged, with or without outpatient follow up. Thakore *et al* showed that adherence to these guidelines in their UK ED population, would have increased hospital admissions by between 38% and 58% (Thakore SB et al).

All guidelines include history, examination and investigation of syncopal patients (Brignole et al 2001, Brignole et al 2004) however only the ACEP guidelines have focussed directly on ED investigations and management (Molzen GW et al, Huff et al). The 2001 ACEP guidelines suggested admission for patients with a history of CCF or ventricular arrhythmias, associated chest pain or other symptoms compatible with acute coronary syndrome, evidence of significant CCF or valvular heart disease on physical examination, or ECG findings of ischemia, arrhythmias, prolonged QT interval, or bundle branch block. These guidelines also suggested that admission should be considered for patients with syncope who are older than 60 years, have a history of coronary artery or congenital heart disease, have a family history of unexpected sudden death, or in younger patients who present with exertional syncope without an obvious benign aetiology.

The ACEP guidelines were recently reviewed (Huff et al) with the 2007 update recommending admission for patients with syncope and evidence of heart failure or structural heart disease, and for those with high risk factors defined as older age and associated comorbidities, abnormal ECG (acute ischemia, arrhythmias or significant conduction abnormalities), haematocrit <30% or history or presence of heart failure, coronary artery disease, or structural heart disease.

Presently it is unclear whether either the application of guidelines to syncope management, or the practice of admitting patients with syncope to hospital has any impact on patient outcome. No such benefits have ever been demonstrated. Brignole et al however have shown that the use of a standardised approach in a syncope unit leads to patients undergoing fewer basic laboratory tests, fewer brain-imaging examinations, fewer echocardiograms, more carotid sinus massage and more tilt table testing compared to patients attending hospitals without such a unit. Patients managed in the syncope unit were 56% more likely to receive a diagnosis of neurocardiogenic syncope (Brignole M et al 2003). Compared to care prior to introduction of the unit, patients were less likely to be hospitalised, had shorter inpatient stays and had fewer tests performed per patient. Orthostatic and neurocardiogenic syncope were also more likely to be diagnosed (Brignole M et al 2006a).

1.14 Conclusions

Identifying a cardiac cause for syncope is a poor prognostic indicator for ED patients presenting with syncope. This is related to the severity of the patient's underlying cardiac disease rather than the syncopal event itself. Patients presenting with syncope who have significant cardiac disease should be investigated thoroughly to determine the nature of the underlying heart disease and the cause of syncope. At present there is little evidence that this improves their dismal prognosis (>30% one year mortality). There are seven risk stratification studies on syncope in the ED. All have used different characteristics and outcome measures in their risk stratification tools. Only two were prospective and have not been successfully externally validated. Prior to this study, none have been examined in a UK population. Presently the ACEP guidelines are the most useful aids to the management of syncope in the ED. None of the syncope guidelines or CDRs have been derived or validated in a UK or Republic of Ireland population, and in the US where many of these tools and guidelines were developed, consensus with regard to a universal approach to patients remains lacking (Grossman SA et al).

Chapter 2

Study aims, Objectives and Research Questions

2.1 Aims

As discussed in the introduction, syncope is a difficult condition to manage in the ED. There have been some attempts to derive CDRs and develop guidelines to aid emergency physicians. The former have not been widely accepted and adopted due to their limitations, which have been discussed. The latter have suffered from the lack of available evidence and are based on existing CDRs and expert consensus.

It was the intention to derive a CDR using characteristics that have been applied in previous rules and also biochemical markers which as yet have not been used in the development of a syncope CDR. The markers that were chosen were D-dimer, troponin I and BNP.

The primary aim of this study was therefore:

To develop and to validate a CDR using history, examination, ECG and biochemical markers, to predict one-month serious outcome and all-cause death in patients presenting with syncope to the ED.

Secondary aims were:

To assess the process of patient recruitment and to test study methodology and feasibility of data collection using a pilot study.

To review the literature to establish current ED syncope management.

To establish the current practice of ED management of syncope in the UK and Republic of Ireland.

To investigate whether improved research based syncope guidelines are required in the UK and Republic of Ireland.
To evaluate what facilities are available in UK EDs to which new guidelines could be tailored.

To compare the performance of existing RIE ED guidelines with existing CDRs at predicting one-month serious outcome and all-cause death in patients presenting with syncope to the ED.

To compare the performance of the ROSE CDR with existing CDRs at predicting one-month serious outcome and all-cause death in patients presenting with syncope to the ED.

To establish whether BNP is a predictor of one-month serious outcome and all-cause death in syncope patients presenting to the ED.

To determine whether BNP predicts one-month serious cardiovascular outcome in patients presenting with syncope to the ED.

To assess the value of a 12-hour troponin I measurement to identify AMI, and to predict one-month serious outcome and all-cause death in patients presenting with syncope to the ED.

To establish whether D-dimer is a predictor of one-month serious outcome and all-cause death in syncope patients presenting to the ED.

To determine the incidence of a raised D-dimer in ED syncope patients.

To determine whether D-dimer predicts one-month serious cardiovascular outcome in patients presenting with syncope to the ED.

2.2 Objectives

To enrol 550 patients into a derivation cohort and a further 550 patients into a validation cohort in order to develop and validate a CDR using history, examination, ECG and biochemical markers in a UK population, to predict one-month serious outcome and all-cause death in patients presenting with syncope to the ED.

To perform a literature review of syncope management related to the ED.

To perform an initial feasibility pilot study using a single cohort of 100 ED patients presenting with syncope over a three month period, in order to assess the process of patient recruitment and to test study methodology and feasibility of data collection prior to the main ROSE study.

To determine the current practice of ED management of syncope in the UK and Republic of Ireland using a postal survey, in order to investigate whether improved research based syncope guidelines are required in the UK and Republic of Ireland, and to evaluate what facilities are available in UK EDs to which new guidelines could be tailored.

To enrol 550 patients into a derivation cohort and a further 550 patients into a validation cohort to compare the performance of the ROSE CDR with both existing CDRs and RIE ED guidelines, and at predicting one-month serious outcome and all-cause death in patients presenting with syncope to the ED.

To determine plasma BNP concentrations in adults presenting to the ED with syncope to establish whether BNP is a predictor of one-month serious outcome and all-cause death and/or one-month serious cardiovascular outcome in patients presenting with syncope to the ED.

To measure plasma troponin I concentrations at 12 hours after syncope in higher-risk admitted patients, and in lower-risk patients, following discharge (between 12 hours

and seven days) who are enrolled into the derivation cohort of the ROSE study in order to assess the value of a 12-hour troponin I measurement to identify AMI, and to predict one-month serious outcome and all-cause death in patients presenting with syncope to the ED.

To determine plasma D-dimer concentrations in adults presenting to the ED with syncope who are enrolled into the derivation cohort of the ROSE in order to determine the incidence of a raised D-dimer in syncope patients, to establish whether D-dimer is a predictor of one-month serious outcome and all-cause death in syncope patients presenting to the ED, and to determine whether D-dimer predicts one-month serious cardiovascular outcome in patients presenting with syncope to the ED.

2.3 Research questions

1. Can a syncope CDR using specific components from the history and examination, ECG characteristics and biochemical markers predict one-month serious outcome and all-cause death in ED patients presenting with syncope?

2. Are biochemical markers better in isolation than history, examination and ECG characteristics at predicting one-month outcome, or are they more useful in conjunction with them to improve the accuracy of a CDR in predicting one-month serious outcome and all-cause death in syncope patients presenting to the ED?

3. What is the current practice of ED management of syncope in the UK and Republic of Ireland?

4. Are improved research based syncope guidelines required in the UK and Republic of Ireland?

5. What facilities are available in UK EDs to which new guidelines could be tailored?

6 How do existing RIE ED guidelines compare with existing CDRs at predicting one-month serious outcome and all-cause death in patients presenting with syncope to the ED?

7 How does the performance of the ROSE CDR compare with existing CDRs at predicting one-month serious outcome and all-cause death in patients presenting with syncope to the ED?

8 Does BNP predict one-month serious outcome and all-cause death in syncope patients presenting to the ED?

9 Can BNP predict one-month serious cardiovascular outcome in syncope patients presenting to the ED?

10 What is the value of a 12-hour troponin I measurement to identify AMI and predict one-month serious outcome and all-cause death in patients presenting with syncope to the ED?

11 Does D-dimer predict one-month serious outcome and all-cause death in syncope patients presenting to the ED?

12 What is the incidence of a raised D-dimer in syncope patients?

13 Can D-dimer predict one-month serious cardiovascular outcome in syncope patients presenting to the ED?

Chapter 3

UK ED survey

3.1 Aims

The management of syncope patients in UK EDs has not yet been established. Only two previous studies have looked at UK practice (Thakore et al, Crane SD) and in the absence of UK guidelines it is not clear what strategies are currently in use to manage patients. It is also important to see what facilities are available to the majority of EDs in order to ensure that any improved assessment strategies are able to be easily implemented.

The aims of this part of the study were therefore:

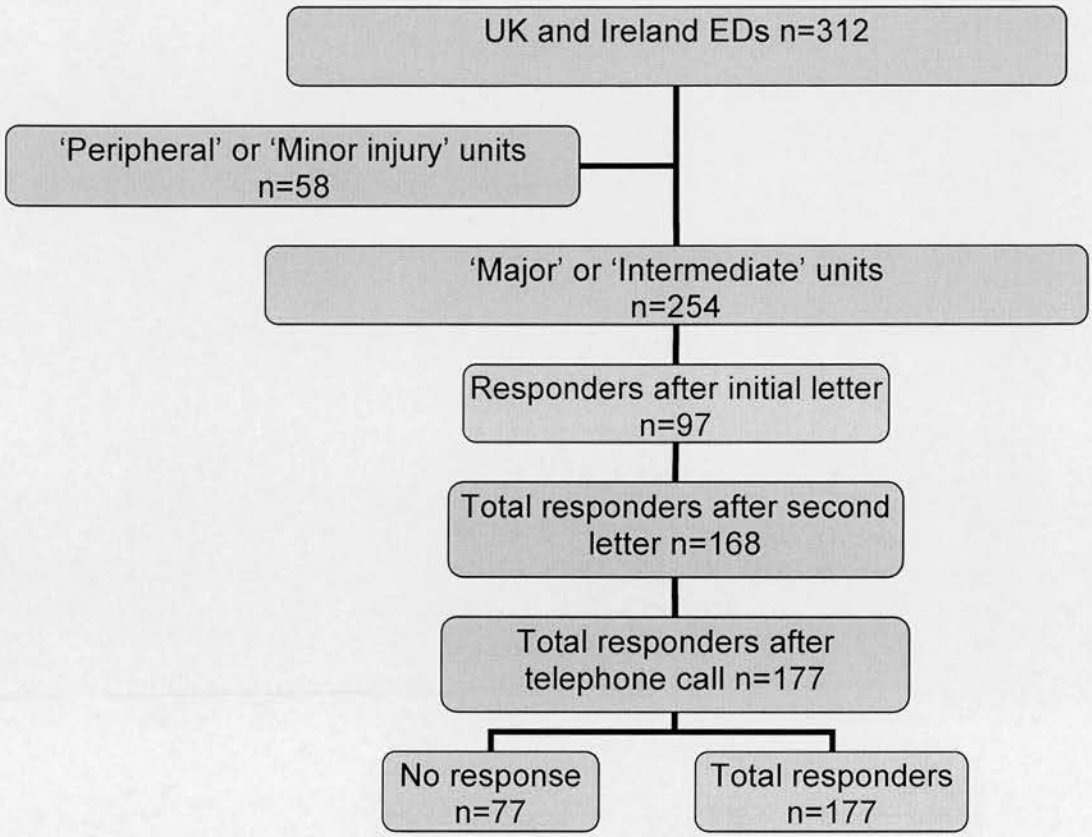
- To establish the current practice of ED syncope management in the UK and Republic of Ireland.
- To investigate whether improved research based syncope guidelines are required in the UK and Republic of Ireland.
- To evaluate what facilities are available in UK EDs to which new guidelines could be tailored.

3.2 Methods

A questionnaire and accompanying letter was designed [see Appendix 8]. An electronic list of all 312 EDs in the UK and Republic of Ireland was obtained from BAEM in September 2007. EDs not listed as 'major' or 'intermediate' in the last BAEM directory were removed leaving 254 EDs. The questionnaire with a covering letter and a pre-paid return envelope was then sent out to a named consultant at each of the 254 EDs. After one month the questionnaire was resent to those EDs that had not initially responded (n=157) this time addressed to 'Nurse in charge'. Finally those EDs that had not responded after two attempts (n=86) were contacted by telephone [Figure 3.1].

This study was designed in accordance with published recommended guidelines for ED questionnaires (Cooke MW et al, Wilson S et al).

Figure 3.1 CONSORT type diagram of study enrolment.



3.3 Results

177 EDs (70%) responded. 32 (18%) have syncope guidelines. Of these, six are based on the ESC guidelines (Brignole M et al 2004, Brignole M et al 2001), four on the ACEP guidelines (Molzen GW et al), six on the ACP guidelines (Linzer M et al 1997a, Linzer M et al 1997b), two on the OESIL syncope score (Colivicchi F et al), three on the SFSR (Quinn JV et al 2004, Quinn JV et al 2006) and eight on 'other', usually an ED consultant personal opinion. Nine EDs gave no response to this question and four guidelines are based on more than one source. Of the 32 EDs with

guidelines, 22 have them in paper form, three in poster format and 12 are in electronic form.

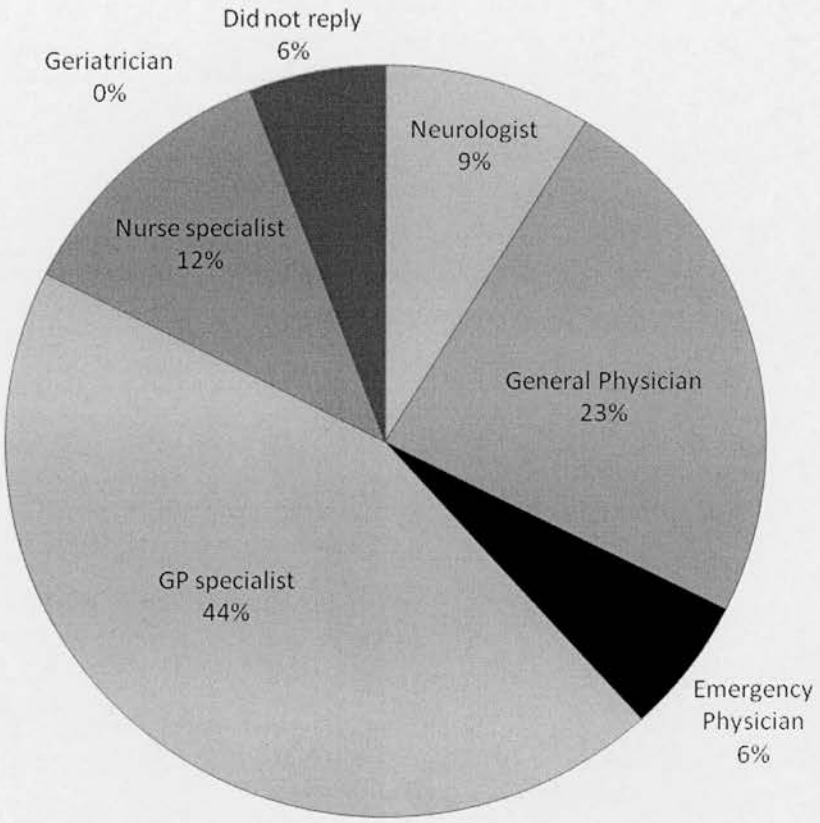
Of the 32 EDs with syncope guidelines, 22 are for ED use only and six are general hospital guidelines. Table 3.1 shows the comparison of EDs with and without syncope guidelines. 97 of 177 EDs (55%) have an observation ward or clinical decision unit. 48 (49%) of these admit syncope patients to it. 32 EDs (18%) have access to a specialist syncope outpatient clinic. 28 of these 32 EDs (88%) can access this clinic from the ED.

Table 3.1 Comparison of EDs with and without syncope guidelines.

	EDs with syncope guidelines (n=32)	EDs without syncope guidelines (n=145)
Does your hospital have single or separate front doors for Medical/GP referral/ED patients?	16 single (50%) 3 no response (9%) 13 separate (41%)	57 single (39%) 7 no response (5%) 81 separate (56%)
Does your ED have an observation ward/clinical decision unit?	18 yes (56%) 14 no (44%)	79 yes (54%) 3 no response (2%) 63 no (43%)
Does your hospital have a specialist syncope outpatient clinic?	10 yes (31%) 1 no reply (3%) 21 no (66%)	22 yes (15%) 5 no reply (3%) 118 no (82%)
Do you think more research based guidelines would be useful when managing patients presenting with syncope to the ED?	24 yes (75%) 3 no reply (9%) 5 no (16%)	120 yes (83%) 6 no reply (4%) 19 no (13%)
Do you have access to near-patient testing in your ED?	14 yes (44%) 2 no response (6%) 16 no (50%)	64 yes (44%) 78 no (54%) 3 no reply (2%)

Figure 3.2 displays which specialty runs this clinic. 78 EDs (44%) have access to near-patient testing in their ED and eight (5%) use BNP testing in their ED.

Figure 3.2 Personnel running syncope outpatient clinic.



3.4 Discussion

This is the first survey to describe the management of syncope in UK emergency medical practice. It clearly shows marked variation in routine practice in the UK and Republic of Ireland. A 70% response rate to the questionnaire was achieved. This compares favourably with similar studies. There is no reason to suspect that these results are not generalisable to all medium and large size UK EDs.

It is of interest how few EDs have syncope guidelines to assist decision-making given the complexity of risk stratification and disposition of this common ED presentation. 81% of EDs however felt that improved research based guidelines would be of use when managing syncope patients. Whilst it was not specifically asked why guidelines were not used, these findings may suggest dissatisfaction with existing guidelines. The lack of a UK ED orientated guideline has led some EDs to

construct their own guidelines based on a variety of sources, whilst others simply have no advice in place. A consensus UK guideline similar to that published by ACEP is clearly required.

18% of EDs have access to a specialised syncope clinic. This is more common in EDs with existing guidelines. It is likely that in these EDs, the clinic forms part of a structured pathway of care with identification of low-risk patients safe to be discharged and medium-risk patients who may be able to go home with early follow-up and investigation. Many EDs have an observation ward or clinical decision unit and many already admit syncope patients to this. There is clearly scope to manage syncopal patients in a similar way to other common conditions such as chest pain with a period of observation, along with risk stratification in the form of echocardiography and biochemical markers. 44% of EDs already use near-patient testing and 5% have access to near-patient brain natriuretic peptide, a biomarker currently undergoing investigation as a syncope biomarker (Reed MJ et al 2007b).

Once completed, the results from the ROSE study, the first UK emergency medicine specific CDR for the management of syncope, could be used to form the basis of a College of Emergency Medicine approved UK syncope guideline. This guideline would utilise existing pathways sent to us from other services in the UK and Republic of Ireland. If the ROSE study safely identifies low risk patients then a robust consensus guideline may also support immediate discharge of certain patient groups who could receive further evaluation in specialist syncope outpatient clinics.

3.5 Conclusion

The ED management of syncope patients in the UK and Republic of Ireland is varied. Only 18% of EDs have specific guidelines for managing this difficult and common condition and only 18% have access to a specialist syncope clinic.

Chapter 4

Pilot and Main Study Methodology

4.1 ROSE Pilot study - Aims

The ROSE PILOT study was conducted as a feasibility pilot for the ROSE study. The secondary aim was to perform a preliminary assessment of the utility of near-patient BNP to predict serious outcome in syncope and decide whether to include it as a predictor variable in the main study.

4.2 Methods - Settings

The ED of the Royal Infirmary of Edinburgh (tertiary centre seeing 110,000 adult attendances per annum).

4.3 Inclusion criteria

Patients presenting with syncope aged 16 years or over were prospectively enrolled into the study. Syncope was defined as a transient loss of consciousness with an inability to maintain postural tone followed by a spontaneous recovery without need for therapeutic or electrical intervention.

4.4 Exclusion criteria

- Patients under 16
- Patients previously recruited
- Patient with a good history of seizure or a prolonged (>15 minutes) post-ictal phase
- Patients unable to give written or verbal consent
- Patients whose collapse was suspected to be due to excessive alcohol consumption
- Near-syncope (i.e. no loss of consciousness)

4.5 Enrolment into pilot study

Eligible patients were flagged at the ED high dependency triage area and a DCF was placed in the patient's records. The treating doctor was responsible for deciding eligibility. Assessment of patients was carried out by routine ED clinical staff. A decision to enrol a patient was not overturned later by the study team. The study team reviewed the notes of any patients who had been initially flagged by the triage nurse, but who were later rejected by the doctor. Only nine patients were rejected in this manner. Reasons for the doctor rejecting a patient were inability to obtain consent, patients being found collapsed for an unknown period of time, or patients presenting with a likely seizure. Written consent was obtained from all enrolled patients. This study received ethical approval from Lothian REC (Reference: 05/S1102/35) on September 27th 2005.

4.6 Assessment

All patients underwent a standardised assessment using 31 pre-determined variables (11 focussed on clinical features, nine on past medical history and 11 concerning current medication), 28 examination variables and 26 ECG variables. These were selected after careful systematic review of the literature to identify characteristics that have previously been shown to be associated with serious outcome. After a full history and examination, all patients underwent a 12-lead ECG, lying standing blood pressures and a 'BM stix' glucose estimation. The patient's ED guideline risk group (high, medium, low) was determined by the study doctor after initial assessment [Table 4.1].

Table 4.1

RIE ED existing syncope guidelines based on the ESC, ACP and ACEP guidelines.

High Risk (Admit)

History findings:

- Palpitations related to syncope
- Associated chest pain
- Associated headache
- Related to exertion
- Family history of sudden death <60
- Previous history of VT/VF/cardiac arrest

Examination findings:

- Systolic Heart murmur heard
- Signs of heart failure present
- Systolic BP < 90mmHg
- Suspicion of PE
- AAA detected
- New neurological signs on examination
- Suspicion of CVA or SAH
- FOB present on PR exam
- Other suspicions of GI bleed

ECG findings:

- Mobitz type II heart block
- Wenkebachs type II heart block
- Bifascicular block
- Complete heart block
- Sinus pause >3 seconds
- NEW ST elevation
- Ventricular tachycardia
- Sinus bradycardia <50
- Sino-atrial block
- QTc > 450 msecs
- NEW T wave / ST segment changes
- Brugadas (ST segment elevation V1-V3)
- Arrhythmogenic right ventricular dysplasia

Medium Risk (Consider discharge with early outpatient review)

History findings:

- Age > 60 years
- No prodromal symptoms
- Previous myocardial infarct
- Known history of valvular heart disease
- Known angina / coronary artery disease
- Known history of CCF

Examination findings

- >20 mmHg drop on standing
- Diastolic Heart murmur heard
- Ventricular pause > 3 seconds on Carotid sinus massage
- Trauma associated with collapse

ECG findings:

- Right bundle branch block
- QRS duration > 120 msecs
- OLD T wave / ST segment changes
- Frequent pre-excited QRC complexes
- Q-waves unchanged from old ECG
- Atrial fibrillation or Flutter
- PR >200 msecs (1st degree heart block)

Low risk (Consider discharge)

- None of the above characteristics

Patients who were medium or high-risk according to RIE ED's existing syncope guidelines also had FBC, urea, creatinine, glucose, electrolytes and CRP measured. These patients also underwent near-patient BNP testing. BNP was measured using a whole blood immunoassay technique utilising the Biosite Triage point of care machine (Biosite Incorporated, US; www.biosite.com). Treating physicians were not blinded to the result of the BNP test. Admitted patients also underwent a laboratory based Troponin I at least 12 hours post syncope at the discretion of the admitting team. Patients still in the ED at 12 hours were defined as admitted. Patients were admitted, referred to MOPD, or discharged according to RIE ED's existing syncope guidelines and the study DCF was completed. Patients admitted to hospital or who attended MOPD underwent evaluation of any clinical or historical findings suggestive of a cause of syncope at the discretion of the treating consultant including 24-hr ECG tape and echocardiography investigations.

4.7 Endpoint measures

Primary outcome: Combination of serious outcome and all-cause death at seven days, one month and three months after ED presentation.

Definition of serious outcome:

(1) AMI as defined by the ESC/ACC/AHA/WHF Universal Definition of Myocardial Infarction 2007 (Thygesen K et al)

(2) Life-threatening arrhythmia (recorded episode of VF, sustained VT>120 beats per minute for more than three beats, ventricular pause greater than three seconds, ventricular standstill or asystole documented on monitor or ECG during ED or inpatient stay or on outpatient Holter monitoring and requiring treatment)

(3) Insertion of a pacemaker, or insertion of an internal cardiac defibrillator device, or a decision that the patient requires such a device within one month of the ED attendance, or subsequent insertion related to index collapse

(4) PE (confirmed on ventilation/quantification scan, CT pulmonary angiography scan or angiography)

(5) Cerebrovascular accident, intracranial haemorrhage or SAH (CT, MRI or LP diagnosis)

(6) Haemorrhage requiring a blood transfusion of two units or more during inpatient stay

(7) Acute surgical procedure or endoscopic intervention or a decision that the patient requires such a procedure, secondary to a suspected cause of syncope.

Once three months had elapsed post ED attendance for all patients, the hospital computer system was interrogated to see whether the patients had returned to any hospital in the Lothian region. The hospital records were acquired and scrutinised for all patients who had attended the ED or MOPD or who had been admitted as an inpatient. Any deceased patient in the Lothian region could be identified via the hospital computer system and hospital records were acquired. Hospital notes were scrutinised to determine patients who had a serious outcome within three months of their attendance to the ED with syncope. All patients could be followed up and all hospital notes and records could be traced. Two recruited patients from outside Lothian were contacted by phoned. Hospital notes were available for all patients.

4.8 Review of missed patients

In order to quantify the number of eligible patients not enrolled into the study, a daily search of all ED EPRs was conducted throughout the study using Business Objects 6.5 (Business Objects Enterprise, US) looking for the keywords 'syncope', 'collapse', 'faint', 'loss of consciousness' or 'loc' appearing anywhere on the EPR. Ethical approval was sought for this process. All EPRs with one of these terms was then hand searched and a decision made by the study researcher (MR) using the notes, about whether a patient had presented with a possible syncopal event and whether or not they had been eligible for enrolment. Out of those eligible for enrolment, it was established how many were successfully enrolled and how many were missed and for what reason (e.g. missed by doctor, refused consent, consent not able to be obtained).

A database was compiled of those patients who were eligible but who were not enrolled along with their demographic details, and these were compared to those patients who were recruited into the study.

4.9 Statistical analysis

All patient data was entered into a specially designed Microsoft Access database (Microsoft Corporation, US) and exported into Microsoft Excel (Microsoft Corporation, US) for statistical analysis. A power calculation was not performed for the pilot study however it was decided that 100 patients would be sufficient for the primary aim. BNP and outcome at 3 months was analysed using a ROC curve. The 'study group' and the 'missed group' were compared using the Chi-squared test and the Mann-Whitney U test, and the 'BNP group' and the 'missed BNP' group were compared using the Fisher exact test.

4.10 Results

99 consecutive adult patients were recruited over a three-month period between 7th November 2005 and 7th February 2006. It was thought that 100 patients had been enrolled however one patient had been erroneously duplicated during data entry. 44 patients were admitted to hospital and 55 were discharged from the ED. Eight of the 11 patients with a serious outcome had this by day seven, and three further patients had developed a serious outcome by three months. In total therefore 11 patients had a serious outcome by three months. Of these, five patients had died and six others had an alternative serious outcome [Table 4.2]. All 11 had been admitted from the ED [Table 4.3]. The percentage risk of serious outcome at seven days, one month and three months was 8.1%, 8.1% and 11.1% respectively.

Table 4.2

Description of the 11 patients with a serious outcome.

Patient Study Number	Age	Sex	Serious outcome	RIE ED guidelines risk group	BNP pg/ml
7	68	M	Extreme bradycardia on 24-hour tape including two pauses of 3.5s and 4.0s. Permanent pacemaker inserted. Alive at three months.	Medium	461
17	71	M	Had AAA repair on day one with good recovery. Presented to ED day 80 with leaking AAA repair. Died in theatre.	High	-
24	90	F	AMI (troponin 14.40). Fast AF Alive at three months.	High	1340
32	67	M	Represented to ED in cardiac arrest day 32. Unsuccessfully resuscitated. Primary cause unknown.	High	2040
43	91	M	Ventricular standstill on ward. Permanent pacemaker inserted. Alive at three months.	High	82.5
52	66	M	Died in hospital on day 79 after a hospital readmission. Cause not identified.	High	26.5
55	76	M	Multiple episodes of VT on ward. Internal defibrillator implanted. Alive at three months.	High	-
59	76	M	Two episodes of ventricular standstill 7s and 5s each on 24hr tape. Diagnosis of episodic CHB made and permanent pacemaker inserted. Alive at three months.	Medium	16.3
63	57	F	Died day six after index hospital admission. Syncope secondary to massive upper gastrointestinal haemorrhage. Patient also had terminal lung cancer.	High	1040
66	74	M	Died day six after index hospital admission of left internal carotid artery thrombosis and left cerebral infarct. Also secondary right-sided bronchopneumonia.	Medium	144
78	81	F	Initial syncope thought secondary to hypotension. Interval 24hr tape showed episodes of fast AF and five prolonged pauses up to 3.6s. Permanent pacemaker inserted. Alive at three months.	Medium	489

Table 4.3

Summary of results.

	Serious Outcome	No Serious Outcome	Total
Total Patients	11 (11%)	88 (89%)	99
Admitted	11 (25%)	33 (75%)	44
Discharged	0 (0%)	55 (100%)	55
High-risk group (based on ED guidelines)	7 (22%)	25 (78%)	32
Medium-risk group (based on ED guidelines)	4 (8%)	47 (92%)	51
Low-risk group (based on ED guidelines)	0 (0%)	16 (100%)	16
BNP not measured	2 (7%)	25 (93%)	27
BNP < 100 pg/ml	3 (6%)	44 (94%)	47
BNP >100 pg/ml	3 (14%)	19 (86%)	22
BNP >1,000 pg/ml	3 (100%)	0 (0%)	3

4.11 Current ED guidelines

32 patients were high-risk, 51 medium and 16 low according to existing RIE ED guidelines. Of the patients having a serious outcome, seven were high-risk, four were medium-risk and none were low-risk. Seven of 32 (22%) high-risk patients, four of 51 (8%) medium-risk patients and none of 16 (0%) low-risk patients had a serious outcome.

19 of the 51 medium-risk patients were admitted to hospital and no patient with a subsequent serious outcome was discharged directly from the ED. Admission of all high-risk patients only (by ED guidelines) would have led to 12 fewer admissions, however four serious outcome patients would have been discharged. Admission of all medium and high-risk patients only would have led to 39 extra admissions but would have detected all serious outcome patients.

4.12 Study recruitment rate and comparison of study group and 'missed' group

263 patients presenting between 7th November 2005 and 7th February 2006 were identified from the EPR search as fitting the study's inclusion criteria. The study therefore managed to recruit 37.6% of patients eligible for inclusion. There were 74 men (45%) and 90 women in the 'missed group' compared to 48 men (48%) and 51 women in the 'study group' (p=0.60, ns, Chi squared). Neither the ages of the 'study group' or 'missed group' were normally distributed. Median age of the 'study group' was 71.0 years (IQR 47-81) and of the 'missed group' was 62.5 (IQR 29-78) (p=0.047, significant at the 5% level, Mann-Whitney U).

4.13 BNP

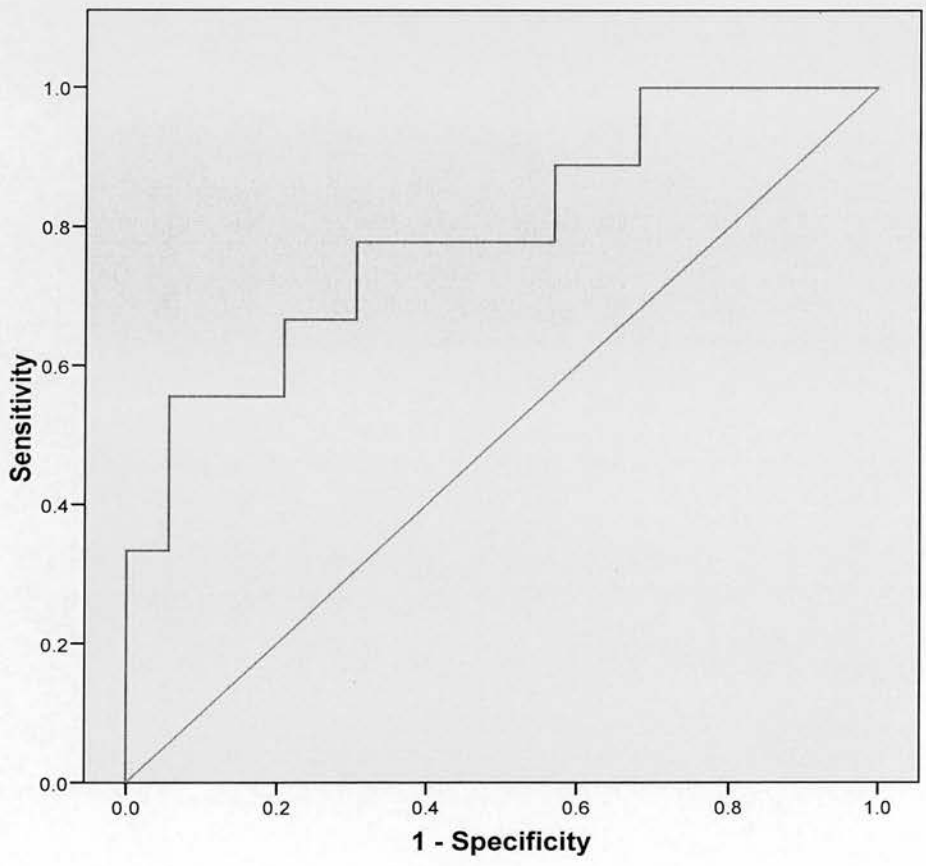
72 of the 82 medium and high-risk patients had BNP measured, nine of whom had a serious outcome (12.5%). The area under the ROC curve of BNP level versus

serious outcome of study patients at three months was 0.79 (95% CI 0.62-0.96) [Figure 4.1]

Those medium and high-risk patients who did not undergo BNP measurement were missed because of either enrolling doctor error (seven patients) or point of care machine or operator error (three patients). The percentage serious outcome in those high and medium-risk patients having BNP measured (72 patients) and the percentage serious outcome in the high and medium-risk patients who did have BNP measured (10 patients) was not significantly different (p=0.617, ns, Fisher exact test). 30 of those admitted had troponin I measured, only one of these was raised (14.40 ng/ml). This was thought to be due to an AMI. Of the 11 patients who developed a serious outcome, six had a troponin measured and in only one was it raised.

Figure 4.1

ROC curve of BNP level versus outcome of study patients at three months.



4.14 Discussion

This study was conducted as a pilot for the ROSE study. It was the first prospective study on syncope within UK ED practice. The primary aim of the study was to assess the process of patient recruitment and to test study methodology and feasibility of data collection prior to the main ROSE study.

This study only recruited 38% of eligible patients. Closer analysis reveals that the 'missed' group had a lower median age than the 'study' group and that the distribution of risk groups was skewed towards the more serious end of the scale. This suggests that treating doctors were not enrolling younger patients with simple low-risk neurocardiogenic syncope which led to a high serious outcome rate. Any CDR derived in a similar population may not be applicable to a low-risk group. Better training of staff and improved methods of recruiting could address this. Using a seven-day event rate of 10%, a power calculation performed to determine sample size requirements for a large prospective derivation and validation study suggested that 500 patients would need to be recruited into a derivation cohort and 500 into a validation cohort. With improved recruitment processes it was thought that this would be feasible over two years.

Of the several CDRs available, some have been derived to predict short-term outcome (seven days) and some to predict long term outcome (12 months). In the pilot study we chose to look at seven day, one month and three month serious outcome. After the pilot this was reviewed and it was decided that a one-month endpoint would be chosen for the main study. The goal of an ED risk stratification tool is to detect patients who are at risk of an imminent serious outcome, the course of which may be altered by early investigation, admission and intervention.

The secondary aim of the study was to assess BNP for inclusion as a predictor variable in the main study. This was the first study to look at using biochemical markers to aid rapid risk stratification of patients presenting to the ED with syncope. It showed that BNP may be a useful predictor of serious outcome in syncope patients presenting to the ED. The advantage of the near-patient test is its immediate availability, which makes it extremely useful for rapid ED decision making.

A proportion of the serious outcomes were expected to include such conditions as ruptured AAAs and SAHs. It was hypothesised that BNP is unlikely to be useful at predicting serious outcome in this non-cardiac syncope group. It was also decided not to measure BNP in patients who were classified as low-risk. This was because of the expected very low rate of serious outcome in this group. Only one patient who had an adverse outcome had a raised troponin I at 12 hours. This suggested that the good BNP sensitivity for serious outcome is not due to it acting as a marker of myocardial ischemia.

There was the potential for work-up bias in the pilot study as some investigations were ordered only on medium or high-risk patients. Work-up (or verification) bias is associated with test validation studies. If the sample used to assess a tool (e.g. a CDR) is restricted to those more likely to have the condition, the sensitivity of the tool can be overestimated. This must be resolved in the main study.

Follow-up of patients involved only interrogation of hospital notes and only two patients were contacted. In the main study this will need to be more thorough with GPs being contacted to ensure complete follow-up of all enrolled patients.

4.15 Conclusions

This pilot demonstrated that a study to derive and validate an ED syncope stratification rule is feasible. The pilot also enabled the study methodology and data collection process to be assessed and revised prior to commencement of the main ROSE study.

Following this pilot, it was thought that BNP may have a role in the risk assessment of syncope patients in the ED and that further work was justified to see how BNP interacts with other clinical variables.

4.16 Main Study Methodology - Setting

See section 4.1.

4.17 Target population

There are ~1,200 patients presenting to the RIE ED per annum who are eligible for enrolment into the study. From the pilot study with improved staff training and recruitment methods it was anticipated that between 800 and 1,000 patients could be recruited per annum.

4.18 Sample size and power calculation

With a sample size of 500 patients and assuming a one-month adverse outcome rate of 10.0% (Reed et al 2006, Reed et al 2007, Quinn et al 2004) at the average value of any predictor variable, then there will be 80% power of showing that this variable has a statistically significant association with 'serious outcome' ($p<0.05$), if the odds ratio for a one SD change in the value of the predictor value is 1.7. The calculation allows for a correlation of this variable with the other covariates such that $r^2=0.3$. If a binary risk factor has a prevalence of 20% there will be an 80% power to detect as statistically significant at the 5% level, an increase from a baseline one-month adverse outcome rate of 10% if the odds ratio is 2.5. If a risk factor has a prevalence

of only 10% there is a corresponding 80% power to detect an odds ratio of 3.2. An expert panel consisting of six representatives from emergency, cardiovascular, general and geriatric medicine, and medical statistics, met in January 2007 to review the selected predictor variables and definitions of all endpoint measures.

4.19 Inclusion criteria

See section 4.3.

4.20 Exclusion criteria

As section 4.4, however relative or guardian written assent also approved by ethics committee for main study. Fourth exclusion criteria for main study therefore:

- Patients unable to give written or verbal consent and without a relative or guardian to give written assent

4.21 Enrolment into derivation study

Potentially eligible patients were flagged in the ED triage area and a DCF was placed in the patient's records. Routine ED clinical staff assessed patients and decided eligibility. A decision to enrol a patient was not overturned later by the study team and enrolled patients were analysed on an intention-to-treat basis.

Because the treating doctor enrolled eligible patients and completed the DCF, there was the potential for selection bias. Sicker patients could have been excluded because of the time required to complete study paperwork. This was addressed by reducing the required paperwork to be completed at the time of enrolment to an absolute minimum. The study researcher (MR) completed the rest of the data collection such as blood results at a later time. The treating doctor completed as much as possible of the DCF at the time of patient enrolment. It is important that

any derived CDR is based on information that is available to the ED doctor at the time of seeing a patient.

Power calculations suggested a minimum requirement of 500 patients in the derivation cohort available for final analysis. As it was anticipated that some patients would be lost to follow-up or not have complete data, therefore it was aimed to recruit a further 10% (i.e. a total of 550 patients) during the nine-month derivation study.

4.22 Assessment

All patients underwent a standardised assessment using 32 pre-determined variables (nine focussed on clinical features, 10 on past medical history and 13 concerning current medication) and 14 examination variables. These were selected after careful systematic review of the literature to identify characteristics that have previously been shown to be associated with serious outcome.

After a full history and examination, all patients underwent a 12-lead ECG, lying standing blood pressures and a 'BM stix' glucose estimation. All patients had two 2.7 ml EDTA, one 4.7 ml Lithium-Heparin-Gel and one 2.7 ml Glucose taken and a FBC, urea, creatinine, glucose, electrolytes, liver function and HS-CRP were formally measured in the hospital laboratory. One 3.0 ml Citrate Coagulation was also taken, spun down in the biochemistry laboratory and the plasma kept for storage. A study label was placed onto the laboratory request form, and samples were sent to the hospital laboratory in the usual manner.

Near-patient BNP testing was performed using a small quantity of blood from the other 'spare' 2.7 ml EDTA sample using the Biosite Triage point of care machine. For any patient in whom the near-patient BNP test was not performed (e.g. physician or machine error) this was performed the following day using the plasma from the patient's original EDTA sample, which was taken on the patient's presentation. This was routinely spun down after testing and stored immediately. Treating physicians

were not blinded to the result of the BNP test however the test was not used routinely in the ED to guide decision making.

Patients were admitted, referred to MOPD, or discharged according to current ED protocols. Patients still in the ED at 12 hours post ED arrival were defined as admitted. Enrolling doctors were not told what serious outcomes measures were being studied. Patients admitted to hospital or attending MOPD underwent evaluation of any clinical or historical findings suggestive of a cause of syncope at the discretion of the treating consultant including 24hr ECG tape and echocardiography investigations.

A review of missed patients was performed as in the pilot study (see section 4.8)

A Microsoft Access database was designed for data entry, which was performed by MR. A separate database was used for derivation and validation cohorts. Data entry was checked and cleaned by one of the study statisticians (RL). The contents of the Microsoft Access database was exported into Microsoft Excel, SPSS (SPSS incorporated, US), and SAS (SAS institute incorporated, US) for statistical analysis by the study statisticians (RP and RL). A patient flow chart was also constructed detailing patient recruitment.

4.23 Endpoint measures

Primary outcome: Combination of serious outcome and all-cause death at one month after ED presentation.

Definition of serious outcome: See section 4.7.

Secondary outcome:

- Syncope related death (death due to a recognised cause of syncope)

- Cardiovascular serious outcome (AMI, life-threatening arrhythmia - recorded episode of VF, sustained VT>120 beats per minute for more than 3 beats, ventricular pause greater than three seconds, ventricular standstill or asystole documented on monitor or ECG during ED or inpatient stay or on outpatient Holter monitoring and requiring treatment, insertion of a pacemaker, or insertion of an internal cardiac defibrillator device, or a decision that the patient requires such a device within one month of the ED attendance, or subsequent insertion related to index collapse)

Outcome, final discharge diagnosis and information regarding inpatient stay, investigations, interventions and serious outcome was identified by way of ED, hospital, Registrar General and GP records, death certificates, post mortem results and via a structured telephone interview with the patient.

4.24 Endpoint review

Initially one investigator (MR) reviewed the notes of all study patients and selected those who had in his opinion had a primary outcome, as well as any others who could in any way be interpreted to have reached this endpoint. A second investigator (AC) then independently reviewed these notes to ensure agreement with the first investigators opinion and any disagreements were resolved initially discussion between MR and AC, and then if necessary by consensus from three other investigators (DN, KJ & AG). All were blinded to the presence or absence of all predictor variables throughout this procedure. Patients who were unable to be followed up were excluded prior to statistical analysis.

Two investigators (MR and AG) then independently reviewed notes of all patients reaching endpoint to determine patients whose cause of syncope was obvious at the time of enrolment in the ED, resolving disagreements by consensus and then if necessary by consensus from three other investigators (DN, AC & KJ).

A cardiologist (JL) and an emergency physician (MR) independently reviewed all ECGs to agree ECG findings. This was done using a standardised assessment of 24 pre-determined ECG variables. These were selected after careful systematic review of the literature to identify characteristics that have previously been shown to be associated with serious outcome. They were blinded to the presence or absence of all predictor variables throughout this procedure. After the ECGs of all patients reaching endpoint were reviewed, these two investigators met to resolve disagreements by consensus.

4.25 Definition of ECG characteristics

Sinus rhythm.....	Visible P waves followed by QRS complex
PR >200 msecs.....	PR interval greater than 200 msecs
Mobitz type II heart block.....	As stated
Wenkebach heart block.....	As stated
Bifascicular block.....	QRS length ≥120 with RBBB and L axis > +90 (RAD) or < -30 (LAD)
Trifascicular block.....	PR interval >200 ms, QRS length ≥ 120 with RBBB and L axis >+90 (RAD) or <-30 (LAD)
CHB.....	No relation between P waves and QRS
Sinus bradycardia <50.....	Sinus rhythm less than 50 beats per minute
Sinus pause >3 seconds.....	As stated
ST elevation >1mm.....	As stated
T wave inversion.....	Except aVR - noted if isolated to lead III or V1
ST segment depression >1mm.....	As stated
Pathological Q-waves.....	25% or more of the height of the partner R wave, > 0.04 s in width and > 2mm in depth
QTc > 450 msecs.....	QTc interval > 450 msecs
Left bundle branch block.....	QRS length > 120 msecs
Right bundle branch block.....	QRS length > 120 msecs
QRS duration ≥ 120 mseconds.....	As stated
Number of ventricular ectopics.....	Number of ventricular ectopics in 10secs
Atrial tachycardia >100.....	Atrial flutter/fibrillation/tachycardia >100 bpm

Narrow complex tachycardia >100... Rate > 100 bpm and QRS ≤ 120 msecs

Broad complex tachycardia >100..... Rate > 100 bpm and QRS length >120 msecs

4.26 Statistical analysis

After derivation data collection, multivariate logistical regression analysis was performed to determine factors associated with endpoints, and a CDR was developed. Previous syncope risk stratification models have either used a stepwise multiple linear logistic regression model, a stepwise Cox proportion hazards model or recursive partitioning. The stepwise procedures can be criticised because they are automatic methods, based on the independent statistical significance of the potential risk factors. Thus a relevant variable may be excluded if it has a moderate correlation with a variable already in the model. Conversely, the large number of risk factors considered also raises issues of multiple testing and the possibility of detecting false positive associations. Recursive partitioning has an even greater risk from false positive findings as the method, in effect, allows for complex interactions among the potential risk factors. The approach chosen was to utilise multiple linear logistic regression but model development was not automatic.

In a preliminary stage of analysis, an attempt to reduce the number of variables using principal component analysis to identify 'factors' among the set of contender variables was made. Thus variables that tend to be mutually correlated will be combined into single variables. Subsequent logistic regression modelling took a knowledge-based approach, incorporating widely accepted risk factors regardless of their statistical significance, while requiring a high level of significance for variables that other studies have found to be unimportant. The biochemical markers were assessed both univariately and also on their ability to add value to the risk stratification based on conventional risk factors. A model was developed for the main outcome variable, from which a practical CDR (the ROSE rule) was formulated. The subjective elements in the model derivation made it particularly important that the model was validated independently.

The validation dataset was obtained while the deviation dataset was being analysed, and no data from it was released until the CDR was finalised. The prospective data collection in this study aimed to minimise the amount of missing data, but for model development, analysis of all subjects is important. For any categorical variables 'missing' was considered as a category, while for continuous variables mean imputation was used in conjunction with a binary dummy variable to indicate whether or not the numerical variable has been imputed.

4.27 Prospective validation

Power calculations suggested a minimum requirement of 500 patients in the prospective validation cohort available for final analysis. It was anticipated that some patients would be lost to follow-up or would not have complete data. It was therefore aimed to recruit a further 10% (i.e. a total of 550 patients) to validate the developed CDR. Statistical analysis was used to assess the CDR performance. An independent clinician (DC) blinded to the ROSE CDR assigned all validation cohort end-points. Patients lost to follow-up were excluded prior to statistical analysis. The sensitivity, specificity, positive and negative predictive values and positive and negative likelihood ratios were calculated for the ROSE CDR in the validation cohort.

4.28 Ethics Committee approval

This study received full ethical approval from the MREC for Scotland A Ethics committee (Reference: 06/MRE00/107) and Lothian REC (Reference: 06/S11ADMIN/151) on January 8th 2007.

Substantial amendment no.1 was approved on 22nd February 2007 and substantial amendment no.2 was approved on 14th May 2007.

Lothian R&D management approval was also obtained on 24th January 2007 (Reference: 2006/R/AE/03).

Substantial amendment no.1 was approved on 6th March 2007 and substantial amendment no.2 on 20th June 2007.

4.29 Informed consent and information sheet

MREC approval was obtained for the study Patient Information Sheet (version 8 - 09/07/2007 - Appendix 6), Patient Information Sheet for Relatives (version 7 – 09/07/2007 - Appendix 7), Patient Consent Form (version 3 – 07/02/2007- Appendix 2), Patient Consent Form for Relatives (version 3 – 07/02/2007- Appendix 3) and GP Information Sheet (version 3 – 24/01/2007- Appendix 4).

Chapter 5

Results: Derivation of the Clinical Decision Rule

5.1 Enrolment

Between 1st March 2007 and 27th October 2007, there were 890 potentially eligible patients out of 70,836 presentations to the ED. 575 patients were screened of whom 13 refused to give consent and 12 were unable to give consent and had no relative or carer who could provide assent. 550 patients were therefore recruited into the derivation cohort. 19 patients were unable to be followed-up [Table 5.1] and two patients had been already previously enrolled into the derivation cohort. 529 patients were therefore available for analysis. A flow chart of patients in the derivation cohort is shown below [Figure 5.1]. Whilst 19 patients were unable to be followed-up it is known from the scope of the Lothian hospital information system that none of these patients represented to any Lothian hospital or died in the community.

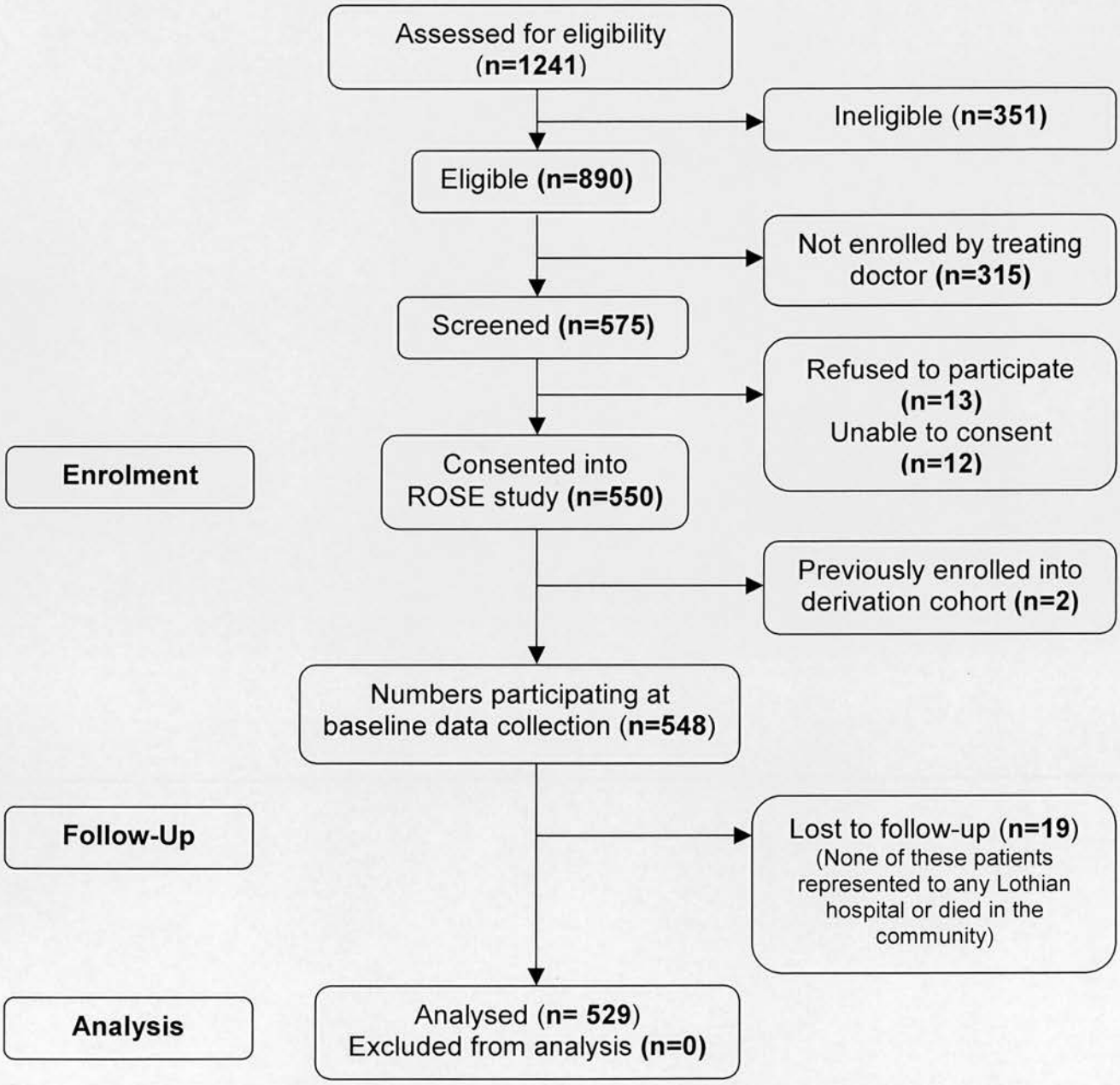
Table 5.1

Reasons for derivation patients not being followed-up

Reason	Number of patients (n=19)
Patient moved address and GP	5
No initial contact details taken at time of recruitment	10
Unable to contact GP or patient at given details	4

Figure 5.1

ROSE derivation STROBE diagram



5.2 Characteristics of derivation followed-up cohort

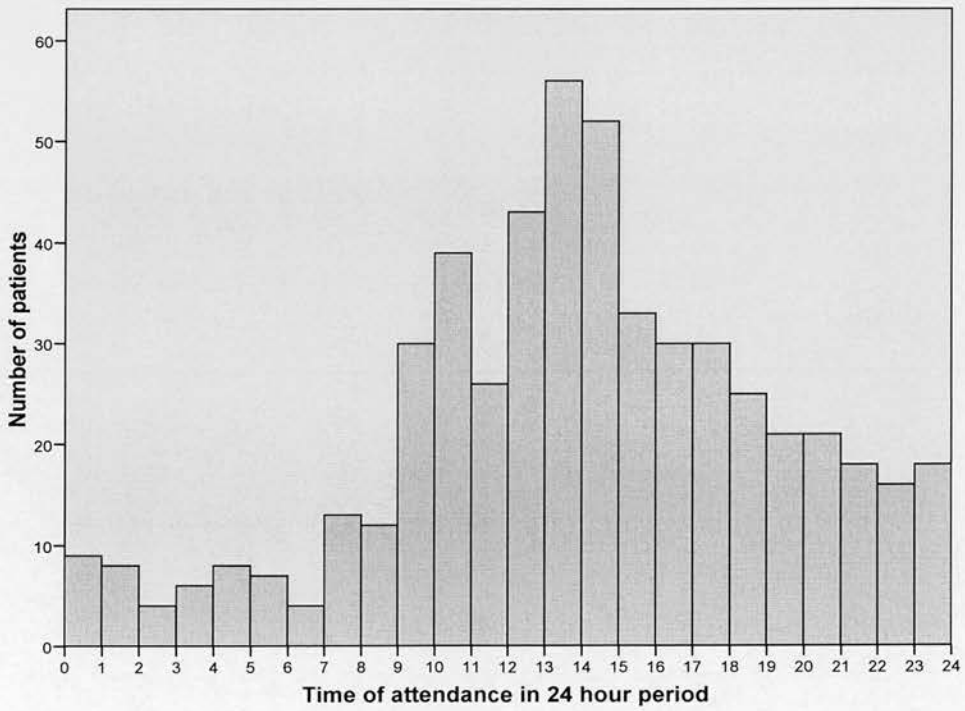
529 patients were able to be followed-up and were available for analysis in the derivation cohort. There were 235 male patients and 294 female patients.

Mean age was 63.8 years (SD 21.2). 252 (47.6%) patients were admitted and 277 (52.4%) were discharged from the ED.

Figure 5.2 shows the time of attendance to the ED for the derivation followed-up cohort

Figure 5.2

Graph to show time of attendance for derivation followed-up cohort (n=529)



5.3 Outcome measures

Primary outcome:

Of the 529 patients who were available for analysis in the derivation cohort, there were 39 patients who had a serious outcome at one month and seven patients who had died within one month. Six patients had both a serious outcome and all cause death at one month.

Secondary outcome:

Of the seven patients who had died within one month, three patients had a syncope related death. 20 patients had a cardiovascular serious outcome [Table 5.2].

Table 5.2

Summary of derivation outcome measures

	Derivation Cohort (n=529)
Primary outcome	40
Serious outcome (SO)	39
All cause death (ACD)	7
Both SO & ACD	6
Obvious diagnosis in ED	17
Secondary outcomes	
Cardiovascular serious outcome	20
Syncope related death	3

Table 5.3 Derivation cohort serious outcomes (n=40)

Patient number	**Primary outcome** (composite endpoint of serious outcome and all-cause death)		**Secondary outcomes**	
	Serious Outcome?	Death within one month?	Cardiovascular serious outcome?	Syncope related death?
3	Ventricular pacemaker insertion	No	Yes	No
10	Pacemaker insertion & complete heart block (CHB)	No	Yes	No
19	Arrhythmia & pacemaker insertion	No	Yes	No
21	≥2 units blood transfused	No	No	No
23	Acute Myocardial Infarction (AMI)	Yes – day 14; AMI	Yes	No
25	≥2 units blood transfused, GI bleed	No	No	No
26	Ventricular Tachycardia (VT)	Yes – day 13; severe pneumonia & VT	Yes	No
30	Large Pulmonary Embolus (PE)	No	No	No
84	Lower gastrointestinal (GI) scope and transfusion	No	No	No
87	Mobitz type 2 block and pacemaker insertion	No	Yes	No
100	Pacemaker inserted	No	Yes	No
124	No serious outcome by definition	Yes – day 15; pneumonia	No	No
125	AICD delivered shock for episode of Ventricular Fibrillation (VF)	No	Yes	No
155	Pacemaker inserted for CHB	No	Yes	No
158	≥2 units blood transfused, GI bleed	No	No	No
189	≥2 units blood transfused, GI bleed	No	No	No
193	Endoscopic procedure	No	No	No
209	VT shocked appropriately by AICD	No	Yes	No
212	Pacemaker inserted for bradycardia	No	Yes	No
228	Pacemaker inserted	No	Yes	No
233	Episodes of VT on 24 hr tape	No	Yes	No
242	Documented arrhythmia	Yes – day 7; tachybradycardia	Yes	Yes
278	Acute on chronic subdural	No	No	No
295	PE diagnosed 19 days later	No	No	No
300	≥2 units blood transfused, GI bleed	No	No	No
302	Pacemaker inserted	No	Yes	No
303	AMI	Yes – day 4; AMI post angiography	Yes	Yes
311	Bilateral PE	No	No	No
316	Bilateral subdural haematomas (SDH)	Yes – day 30; alcoholic liver disease & bilateral SDHs	No	No
369	AMI	No	Yes	No
375	Temporary pacing wire for asystole	No	Yes	No
404	AMI	Yes – day 7; cardiogenic shock due to AMI	Yes	Yes
408	AMI	No	Yes	No
409	≥2 units blood transfused	No	No	No
418	≥2 units blood transfused	No	No	No
488	PE	No	No	No
500	Endoscopy - severe reflux oesphagitis	No	No	No
512	CT guided biopsy of tumour	No	No	No
529	Needle biopsy of lung tumour	No	No	No
530	Laparotomy for perforated caecal carcinoma	No	No	No

5.4 Derivation study recruitment rate

890 patients presenting between 1st March 2007 and 27th October 2007 were identified from the EPR search as potentially eligible for inclusion into the derivation study. 575 patients were screened for inclusion (64.6%) and 550 were enrolled. 61.7% of patients eligible for inclusion during this derivation time period were therefore enrolled into the study.

5.5 Comparison of derivation cohort enrolled patients and derivation cohort eligible but not enrolled patients

Table 5.4 compares enrolled patients and eligible but not enrolled patients in the derivation study cohort. Enrolled patients in the derivation cohort were significantly younger than those that were eligible but not enrolled in the derivation cohort (p=0.002). There were no significant differences in the sex ratio, admission or death rates. Some bias may have been introduced into the derivation cohort as younger patient were less likely to be enrolled. This may have been because physicians did not include every young patient who presented with neurocardiogenic syncope, however older patients who were more likely to have serious pathology were included.

Table 5.4 Comparison of derivation cohort enrolled patients and derivation cohort eligible but not enrolled patients

	Enrolled n=550	Not-enrolled n=340	p
Mean age (SD)	63.9 (21.6)	58.2 (24.3)	0.002 [a]
Male sex (%)	247 (45%)	141 (41.5%)	0.35 [b]
Admitted (%)	254 (46%)	178 (52.4%)	0.09 [b]
Discharged (%)	296 (54%)	162 (47.6%)	
Death (%)	7 (1.3%)	10 (2.9%)	0.13 [b]

[a] Students t-test (2-tailed) [b] Chi squared with Yates' continuity correction

Figure 5.3

Age distribution of derivation cohort enrolled patients (n=550)

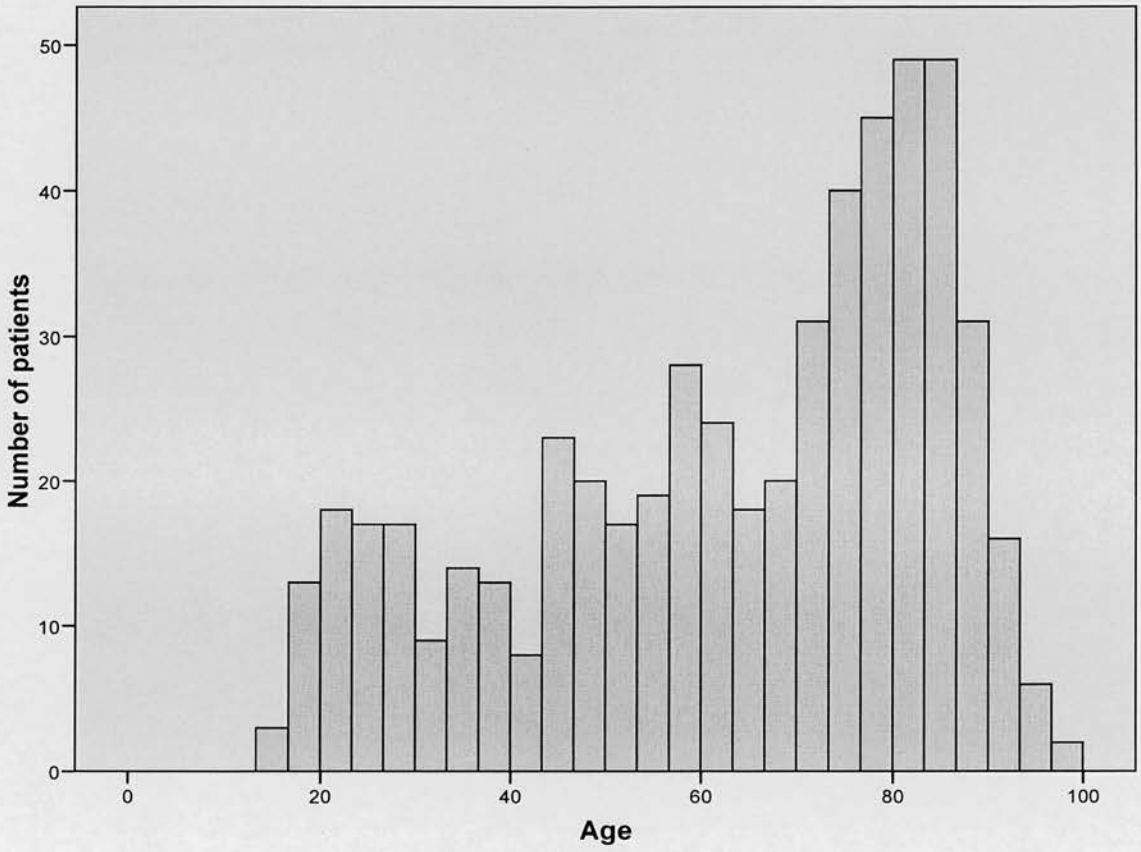
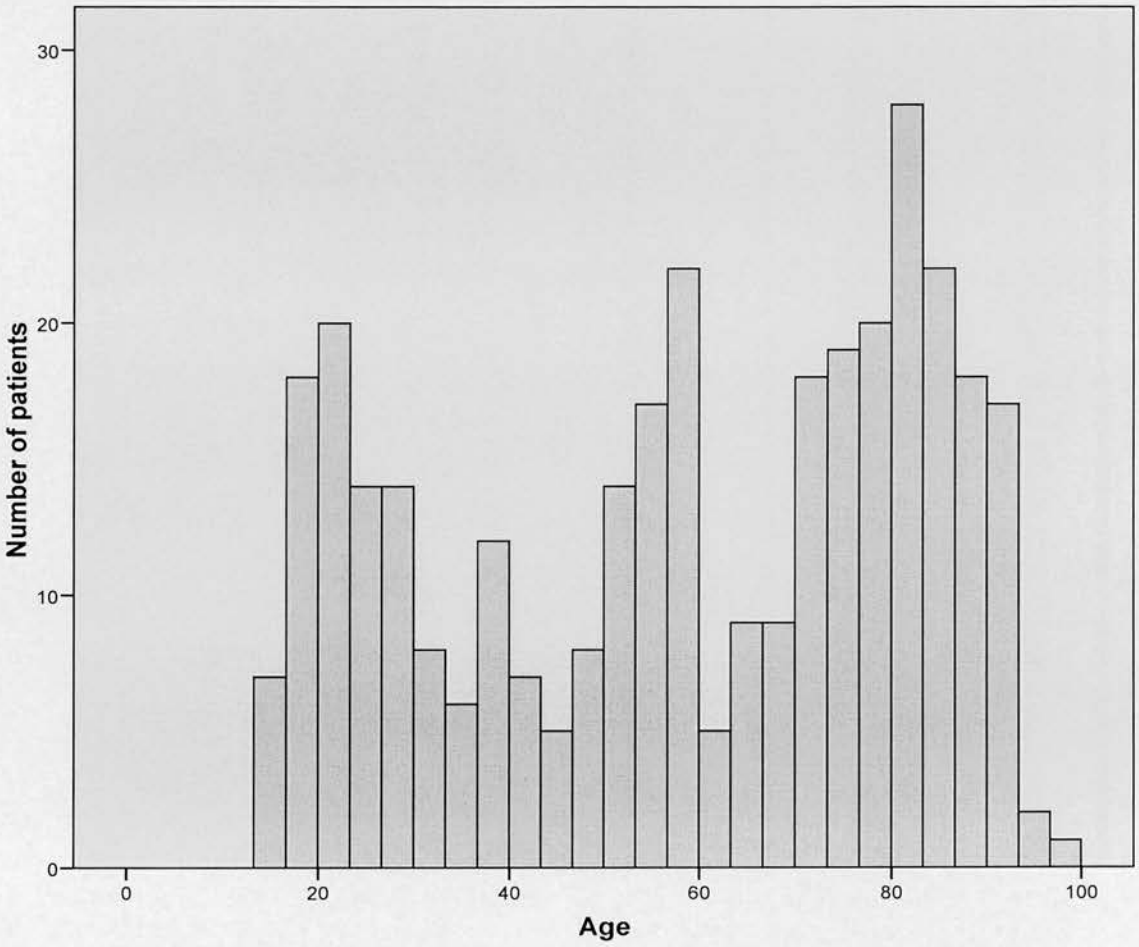


Figure 5.4

Age distribution of derivation cohort not-enrolled patients (n=340)



5.6 Inter-observer reliability of ECG interpretation

Of the 548 patients participating at baseline data collection in the derivation cohort, ECGs were available for 511 with 37 missing. There were no discrepancies in the ECG report between the emergency medicine physician and the cardiologist in 473 of the 511 ECGs (92.6%). Table 5.5 details the ECG interobserver agreement.

Table 5.5

Summary of derivation ECG interobserver agreement

	Number of positives	Number agreed	Number disagreed	Kappa (95% CI)	Agreement
Sinus rhythm	469	509	2	0.98 (0.94-1.0)	0.996
PR >200 msecs	68	510	1	0.99 (0.98-1.0)	0.998
Mobitz type II heart block	0	511	0	1	1
Wenkebach heart block	0	510	1	0	0.998
Bifascicular block	6	511	0	1	1
Trifascicular block	0	511	0	1	1
Complete heart block	1	511	0	1	1
Sinus bradycardia <50	12	510	1	0.96 (0.88-1.0)	0.998
Sinus pause >3 seconds	0	511	0	1	1
ST elevation >1mm	17	501	10	0.68 (0.49-0.87)	0.98
T wave inversion	287	507	4	0.98 (0.97-1.0)	0.992
ST segment dep >1mm	30	506	5	0.91 (0.83-0.99)	0.990
Pathological Q-waves	121	498	13	0.93 (0.89-0.97)	0.975
QTc > 450 msecs	71	511	0	1	1
Left/Right bundle branch	27	509	2	0.96 (0.91-1.0)	0.996
QRS duration $\geq$ 120 msecs	27	510	1	0.98 (0.94-1.0)	0.998
Number of vent ectopics	-	508	3	-	0.994
Atrial tachycardia >100	11	511	0	1	1
Narrow complex tachy >100	31	511	0	1	1
Broad complex tachy >100	1	511	0	1	1

Chapter 6

Results - The ROSE Rule

6.1 Development of the ROSE Clinical Decision Rule

Validation data collection continued from derivation data collection without a break and the ROSE CDR was devised during validation data collection. The derivation cohort database was cleaned and closed prior to analysis. Some continuous variables were also dichotomised e.g. heart rate was included as a continuous variable but also as two categorical variables i.e. <50 and >100. This was to take into account any possible non-linear associations with outcome. This approach was considered for all variables in which it was thought that such an association may exist, however such association was not formally tested for in all predictor variables.

Initially a principal component analysis was performed in an attempt to reduce the number of variables to be considered. This method involves a mathematical procedure that transforms a number of possibly correlated variables into a smaller number of uncorrelated variables called principal components. The first principal component accounts for as much of the variability in the data as possible, as does each succeeding component. Principal component analysis provides a concise overview of a dataset, however in our study this approach did not prove to be helpful.

Mean values and mean differences were calculated for continuous variables for serious and non-serious outcome groups and a t-test was used to determine which continuous variables showed statistical significance. After these variables were scrutinised to determine variables that were clinically sensible, cross tabulation was then performed to look for suitable cut off points attempting to maximise specificity without losing much in the way of sensitivity. For categorical data, cross tabulation was performed, a chi squared test was used to determine which categorical variables showed statistical significance and these were then examined to exclude those variables that were not clinically sensible. As any missing variables for a subject causes that subject to be totally omitted in multivariable analyses, missing continuous

data points were assigned a value corresponding to the mean and missing categorical data points were assigned a value of 'not present'.

Multiple logistic regression analysis was then performed on all significant continuous and categorical variables and those with large relative risk as well as other non-significant but clinically sensible ones to determine independent predictors of serious outcome. Some of these predictors were then amalgamated prior to assigning a weighted integer risk score based on the coefficient derived from the logistic regression analysis. The combination of characteristics chosen along with their risk score were then used to derive a total risk score, which was then applied to the derivation cohort. At this point the study investigators met to review the findings. It was decided that this approach was not sensitive enough or clinically sensible. A patient with only one positive predictor might not score enough to be admitted despite a good predictor of serious outcome or death being present. It was decided by the study investigators that a decision tree approach should be tried, starting with the variables identified from the logistic regression. Variables that predicted adverse outcome were progressively identified in order to optimise the sensitivity of the rule. This approach proved to be both clinically and numerically satisfactory when applied to the derivation cohort and was therefore finally accepted as the ROSE CDR.

6.2 Results

The results of univariate analyses of the association between each predictor variable and serious outcome is shown in Table 6.1.

Table 6.1

The results of univariate analyses of the association between each predictor variable and serious outcome, showing characteristics significant at $p<0.1$.

Characteristic/predictor variable	Univariate p value
Known ischemic heart disease	<0.001 [2]
Previous acute Myocardial Infarction	<0.001 [2]
Amiodarone	<0.001 [2]
% SpO_2 on room air	<0.001
FOB present on PR if indicated	<0.001 [2]
Melena present on PR if indicated	<0.001 [2]
BNP	<0.001 [2]
Haemoglobin / g/L	<0.001 [1]
Haematocrit / ratio	<0.001 [1]
Left BBB	<0.001 [2]
Urea / mmol/L	0.001 [1]
ALP / U/L	0.001 [1]
GGT / U/L	0.001 [1]
Albumin / g/L	0.001 [1]
Implanted internal defibrillator	0.003 [2]
ACE inhibitor / A2 blocker	0.004 [2]
Pathological Q-waves	0.004 [2]
>20mmHg postural drop	0.005 [2]
ALT / U/L	0.006 [1]
Complete heart block	0.008 [2]
Broad complex >100	0.008 [2]
Blood sugar/mmol/L	0.009 [1]
Age	0.01 [1]
Warfarin	0.01 [2]
K+ / mmol/L	0.013 [1]
HsCRP / mg/L	0.016 [1]
Na+ / mmol/L	0.017 [1]
Diuretics	0.018 [2]
QRS ≥120 msecs	0.023 [2]
Neutrophils / $x10^9$/L	0.024 [1]
Male sex	0.028 [2]
Aspirin	0.028 [2]
Glucose / mmol/L	0.032 [1]
Known history of cardiac failure	0.035 [2]
Implanted pacemaker	0.035 [2]
ST segment depression	0.047 [2]
Lymphocytes/ $x10^9$/L	0.051 [1]
QTc Int / msecs	0.053 [1]
Sinus rhythm	0.056 [2]
QTc>450 msecs	0.056 [2]
Related to exertion	0.061 [2]
QRS axis	0.063 [1]
Bilirubin / umol/L	0.07 [1]
eGFR / ml/min	0.075 [2]
Beta blocker	0.09 [2]
Creatinine / umol/L	0.097 [1]

[1] Student t-test [2] Chi-squared test

Variables found in the multiple logistic regression model to be independent predictors of serious outcome in order of statistical significance are shown in Table 6.2

Table 6.2

Variables found to be independent predictors of serious outcome in the multiple logistic regression model, in order of statistical significance

Variables	Wald X^2	Odds ratio (95% CI)
Near patient BNP level ≥ 300pg/ml	15.9	7.3 (2.8-19.5)
Rectal examination showing faecal occult blood	13.6	13.2 (3.4-51.8)
Haemoglobin ≤90 g/l	11.0	6.7 (2.2-20.4)
ECG finding of Q wave(s)	5.8	2.8 (1.2-6.4)
ECG finding of left bundle branch block	5.3	4.8 (1.3-18.2)
Male sex	5.2	2.6 (1.1-6.1)
Oxygen saturation ≤94% on room air	5.1	3.0 (1.2-7.8)
Albumin<37 g/L	2.9	3.2 (0.8-12.4)
White cell count >14 x 10^9/L	2.5	2.4 (0.8-6.8)

Associated seizure activity and PR interval <200msecs were not significant in the univariate analysis but were identified as significant in the stepwise multiple logistic regression. These however were both removed on clinical grounds. Seizure activity was only recorded in 11 patients in the derivation cohort and commonly implies a

neurological condition such as epilepsy rather than other conditions that may lead to serious outcome. A PR interval > 200msecs implies first degree heart block, a benign condition. Whilst a very short PR interval may be pathological (PR interval < 120msecs), a PR interval > 200msecs is defined as normal and not likely to be useful as a predictor of serious outcome.

Using a decision tree approach 'BNP level ≥ 300pg/ml' was used as the first branch accounting for 13 of 40 patients with death or serious outcome. Next, 'rectal examination showing faecal occult blood' was used as the second branch accounting for a further eight patients. A third branch using 'haemoglobin <90 g/l' accounted for four more patients and 'oxygen saturation ≤94% on room air' removed another four as a fourth branch. When 'Q wave' was studied 'Q wave not in lead III' was as sensitive but much more specific than 'Q wave in any lead'. As a 'Q wave in lead III' is sometimes accepted as a normal finding 'ECG finding of Q wave not in lead III' was used as a fifth branch which removed three more patients. Analysis of the remaining eight patients showed that two other variables, 'chest pain associated with syncope' and 'bradycardia ≤50 in ED or pre-hospital' left just three patients not picked up by the previous five branches. Age was found to be significant univariately, but when tested in the multiple logistic regression model it gave a non-significant p value of 0.56. On looking at the stepwise fitting, the big drop in the significance came when BNP was added to the model.

This approach was felt to be clinically sensible as BNP, bradycardia and Q wave mainly identified patients with a cardiovascular outcome (a cardiovascular bundle), rectal examination and haemoglobin identified GI bleeding and other sources of hypovolemic shock, requirement for blood transfusion and endoscopic procedure (gastrointestinal/shock bundle) and chest pain and oxygen saturations identified PE (respiratory bundle). BNP also identified all patients who had left bundle branch block therefore this variable was not included. The three remaining serious outcomes were an endoscopy procedure showing severe reflux, a CT guided biopsy procedure and a pacemaker placed for persistent life affecting neurocardiogenic syncope. Whilst being defined as 'serious' by the study protocol it was felt by the study investigators that these outcomes were not life threatening and the group were not concerned that these were missed by the ROSE rule.

The ROSE rule was therefore finalised as follows:

Figure 6.1 The ROSE Rule

	Admit if <u>any</u> of the following are present:
B	B NP level ≥ 300pg/ml
	B radycardia ≤50 in Emergency Department or pre-hospital
R	R ectal examination showing faecal occult blood (if indicated)
A	A naemia - Haemoglobin ≤90 g/l
C	C hest pain associated with syncope
E	E CG showing Q wave (not in lead III)
S	S aturation ≤94% on room air

A patient should be considered high risk for serious outcome and admitted if any one of the seven characteristics is present.

6.3 Performance of ROSE rule in derivation cohort

The sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios of the ROSE rule in the derivation cohort were 92.5%, 73.8%, 22.4%, 99.2%, 3.5 and 0.1 respectively. The rule missed three patients (two of whom were admitted) compared to five patients with serious outcomes who were discharged from the ED (four of whom would have been identified by the ROSE rule) and would have potentially saved 87 admissions in the derivation cohort.

Table 6.3 Use of ROSE rule in derivation group

One or more ROSE rule characteristic present?	Serious Outcome		Total
	No	Yes	
No	361	3	364
Yes	128	37	165
Total	489	40	529

Table 6.4

Comparison of serious outcomes and decision to admit in derivation study

Patient admitted?	Serious Outcome		Total
	No	Yes	
No	272	5	277
Yes	217	35	252
Total	489	40	529

Five patients with serious outcomes were discharged from the ED; these were patient numbers 3,212,302,375 and 529.

Table 6.5

Performance of ROSE rule compared to decision to admit in derivation cohort.

	Current physician performance in derivation cohort (i.e. admission)	ROSE rule
Sensitivity % (CI)	87.5% (72-95)	92.5% (79-98)
Specificity % (CI)	55.6% (51-60)	73.8% (70-78)
Positive predictive value % (CI)	13.9% (10-19)	22.4% (16-30)
Negative predictive value % (CI)	98.2% (96-99)	99.2% (97-100)
Positive likelihood ratio (CI)	2.0 (1.7-2.3)	3.5 (3.0-4.2)
Negative likelihood ratio (CI)	0.2 (0.1-0.5)	0.1 (0-0.3)

The ROSE rule would therefore potentially save 87 admissions and pick up two more serious outcomes compared to physician performance in the derivation cohort.

Chapter 7

Results: Validation of the Clinical Decision Rule

7.1 Enrolment

Between 27th October 2007 and 22nd July 2008, there were 1374 potentially eligible patients out of 74,840 presentations to the ED. 579 patients were screened of whom 16 refused to give consent and 13 were unable to give consent and had no relative or carer who could provide assent. 550 patients were therefore recruited into the validation cohort [Figure 7.1]. 10 patients were unable to be followed-up [Table 7.1], one patient had been already previously enrolled into the validation cohort and one patient later withdrew consent. Whilst 10 patients were unable to be followed-up it is known from the scope of the Lothian hospital information system that none of these patients represented to any Lothian hospital or died in the community.

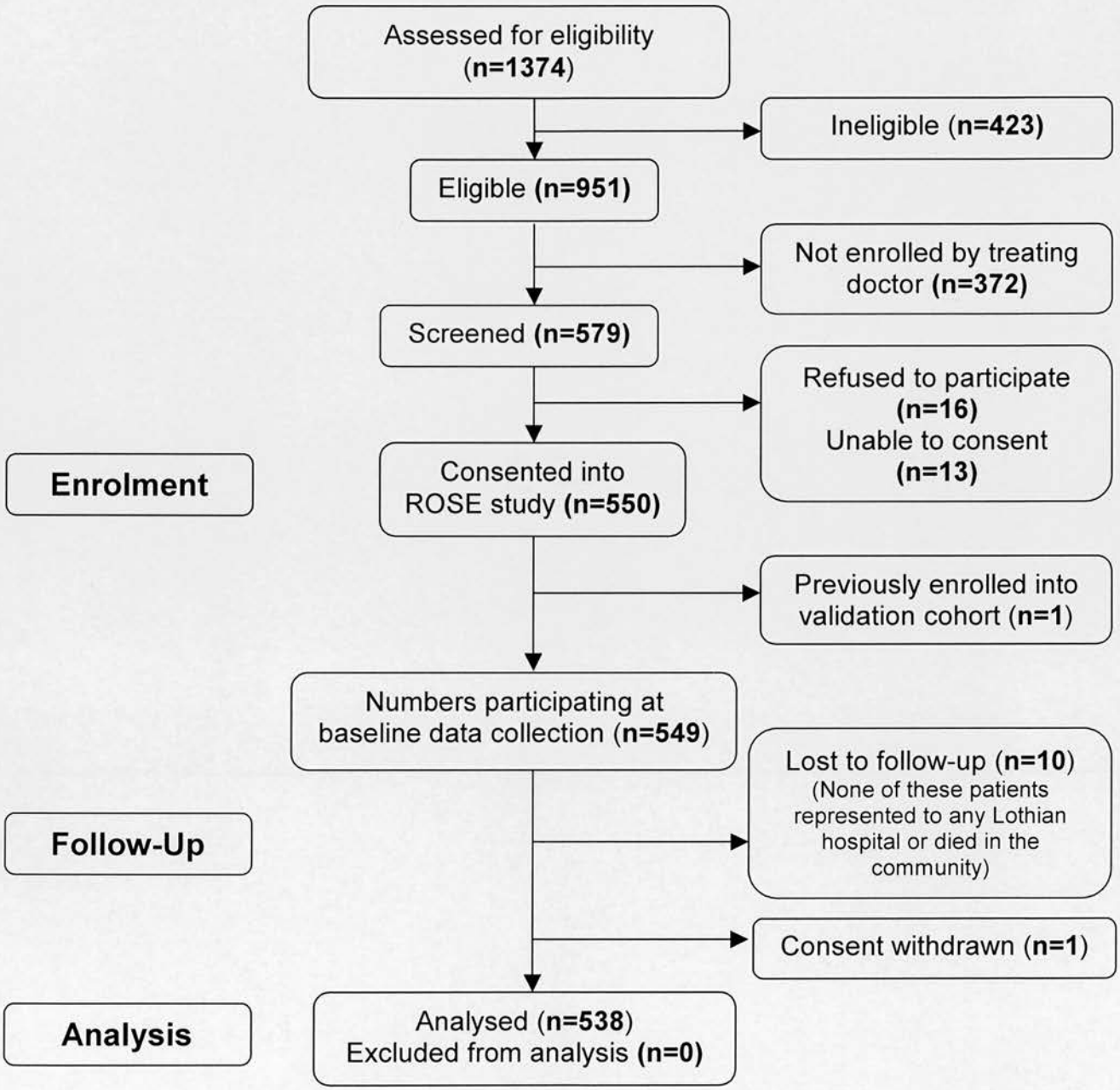
Table 7.1

Reasons for validation patients not being followed-up

Reason	Number of patients (n=10)
Patient moved address and GP	0
No initial contact details taken at time of recruitment	10
Unable to contact GP or patient at given details	0

Figure 7.1

ROSE validation STROBE diagram



7.2 Characteristics of validation followed-up cohort

538 patients were available for analysis in the validation cohort. There were 245 male patients and 293 female patients.

Mean age was 62.4 years (SD 21.9). 286 (53.2%) patients were admitted and 252 (46.8%) were discharged from the ED. Figure 7.4 shows the time of attendance to the ED for the validation cohort followed-up patients.

7.3 Characteristics and comparison of derivation and validation analysed patients

Table 7.2 compares the characteristics of the derivation and validation cohorts analysed patients.

Table 7.2

Characteristics and comparison of derivation and validation analysed patients

Characteristic	Derivation Cohort	n	Validation Cohort	n
Demographics				
Age [1]	63.8 (21.2)	529	62.4 (21.9)	538
Male sex [2]	235 (44.4)	529	24 5 (45.5)	538
Management				
Admitted from ED [2]	252 (47.6)	529	286 (53.2)	538
Medical history				
Previous history of syncope [2]	228 (43.4)	525	214 (39.9)	537
>1 episode in previous year [2]	93 (17.7)	524	83 (15.5)	537
Hypertension [2]	206 (39.0)	528	203 (37.9)	536
Known ischemic heart disease [2]	122 (23.1)	529	109 (20.4)	535
Previous acute Myocardial Infarction [2]	55 (10.4)	529	60 (11.2)	535
Known valvular heart disease [2]	29 (5.5)	528	31 (5.8)	536
Previous cardiac arrest [2]	6 (1.1)	529	6 (1.1)	536
Known history of cardiac failure [2]	27 (5.1)	529	20 (3.7)	535
Implanted pacemaker [2]	5 (0.9)	529	13 (2.4)	537
Implanted internal defibrillator [2]	4 (0.8)	529	3 (0.6)	537
Current medication				
Diuretics [2]	147 (27.8)	529	141 (26.8)	527
Sublingal GTN or GTN spray [2]	68 (12.9)	529	64 (12.1)	527
Longer acting nitrates [2]	32 (6.0)	529	35 (6.6)	527

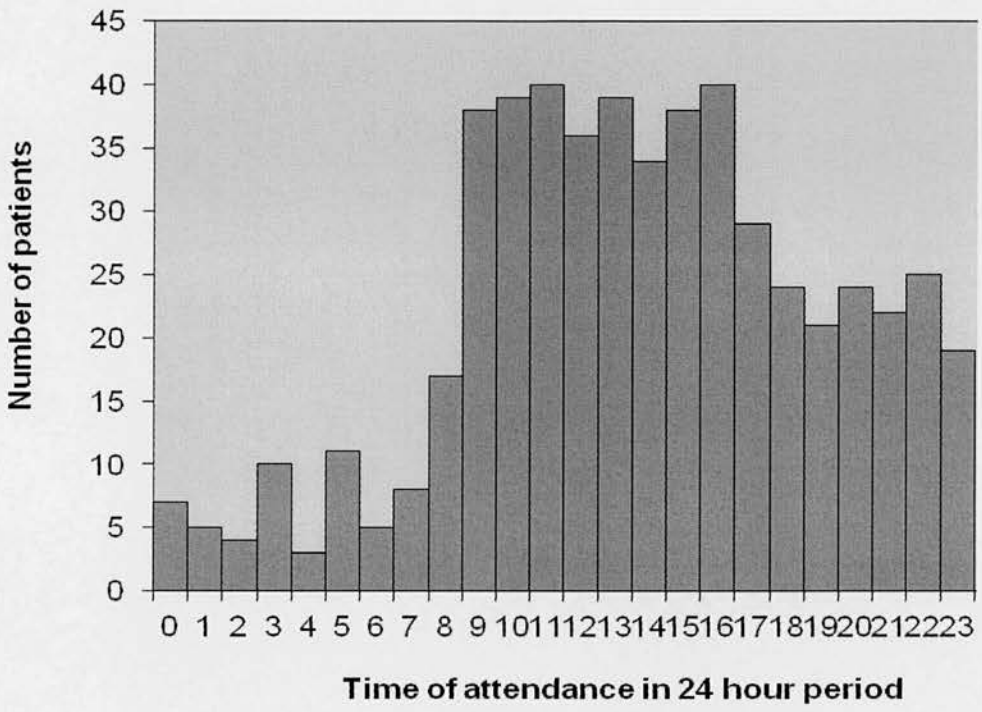
Calcium channel blocker [2]	75 (14.2)	529	69 (13.1)	526
Beta blocker [2]	103 (19.5)	529	109 (20.7)	526
ACE inhibitor / A2 blocker [2]	131 (24.8)	529	140 (26.6)	526
Nicorandil [2]	15 (2.8)	529	14 (2.7)	526
Amiodarone [2]	15 (2.8)	529	4 (0.8)	527
Digoxin [2]	29 (5.5)	529	16 (3.0)	527
Alpha blockers [2]	20 (3.8)	529	21 (4.0)	525
Warfarin [2]	30 (5.7)	529	16 (3.0)	527
Aspirin [2]	146 (27.7)	528	148 (28.1)	526
History of syncope episode				
Associated chest pain [2]	39 (7.4)	529	47 (8.7)	538
Prodromal symptoms [2]	326 (61.6)	529	326 (60.7)	537
Associated palpitations [2]	20 (3.8)	529	15 (2.8)	538
Associated subjective SOB [2]	60 (11.3)	529	50 (9.3)	538
Associated headache [2]	55 (10.4)	529	46 (8.6)	538
Associated situational symptoms [2]	43 (8.1)	529	59 (11.0)	538
Associated with GTN use [2]	17 (3.2)	529	14(2.6)	538
Witnessed seizure activity [2]	11 (2.1)	529	8(1.5)	537
Related to exertion [2]	30 (5.7)	529	31 (5.8)	537
Examination findings				
Pulse / bpm [1]	76.1 (18.3)	527	76.2 (17.1)	537
Temperature / °C [1]	36.4 (0.7)	514	36.6 (0.7)	518
Systolic BP/ mmHg [1]	130.9 (24.0)	525	129.7 (24.2)	534
Diastolic BP/ mmHg [1]	68.1 (12.7)	524	67.4 (13.3)	534
>20mmHg postural drop [2]	50 (14.1)	355	38 (10.6)	358
% SpO_2 on room air [1]	97.2 (2.2)	517	96.8 (3.4)	523
Initial GCS=15 [2]	513 (97.9)	524	516 (98.1)	526
Initial GCS=14 [2]	11 (2.1)	524	9 (1.7)	526
Initial GCS=13 [2]	0	524	1 (0.2)	526
Blood sugar/mmol/L [1]	6.9 (2.1)	492	6.9 (2.5)	496
Heart murmur heard [2]	65 (12.6)	516	71 (13.4)	531
Signs of heart failure [2]	34 (6.5)	523	37 (6.9)	534
New neuro signs [2]	7 (1.3)	527	9 (1.7)	533
FOB present on PR if indicated [2]	16 (19.3)	83	3 (5.3)	57
Melena present on PR if indicated [2]	5 (6.1)	82	0 (0)	62
Associated trauma [2]	167 (31.7)	526	149 (27.9)	534
Syncope cause identified in ED [2]	234 (44.2)	529	219 (40.7)	538
Syncope cause finally identified [2]	348 (65.8)	529	347 (64.9)	535
Arrhythmia in ED [2]	6 (1.1)	529	4 (0.7)	538
Laboratory results				
BNP <5 pg/ml [2]	39 (7.8)	503	80 (16.0)	499
Haemoglobin / g/L [1]	131.0 (17.9)	523	133.3 (16.4)	525
Haematocrit / ratio [1]	0.39 (0.05)	523	0.39 (0.04)	525
Lymphocytes/ $x10^9$/L [1]	9.4 (3.5)	523	9.6 (3.8)	525
Neutrophils / $x10^9$/L [1]	7.10 (3.3)	523	7.2 (3.4)	525
Platelets / $x10^9$/L [1]	242.0 (73.1)	521	237.1 (69.6)	525
Urea / mmol/L [1]	6.8 (3.7)	523	6.8 (4.2)	528
Creatinine / umol/L [1]	104.0 (46.2)	523	106.4 (53.5)	528

eGFR ≥60 / ml/min [2]	359 (67.6)	523	360 (68.7)	524
Na+ / mmol/L [1]	137.7 (3.9)	519	138.2 (3.7)	525
K+ / mmol/L [1]	4.0 (0.5)	519	4.1 (0.5)	525
Bilirubin / umol/L [1]	11.7 (16.0)	514	10.5 (5.5)	522
ALT / U/L [1]	23.9 (26.1)	514	25.0 (23.7)	522
ALP / U/L [1]	84.7 (38.3)	514	86.3 (47.9)	522
GGT / U/L [1]	42.3 (103.9)	514	38.0 (73.5)	522
Albumin / g/L [1]	40.5 (4.1)	521	41.2 (3.8)	528
HsCRP / mg/L [1]	13.8 (40.8)	485	12.6 (29.2)	472
Glucose / mmol/L [1]	6.4 (1.7)	515	6.5 (2.3)	517
Mg2+ / mmol/L [1]	0.84 (0.15)	465	0.84 (0.11)	420
PO4- / mmol/L [1]	1.02 (0.23)	499	1.02 (0.28)	497
Ca2+ / mmol/L [1]	2.34 (0.16)	509	2.36 (0.13)	514
ECG findings				
Rate / bpm [1]	73.8 (18.2)	494	74.0 (16.7)	491
QRS axis [1]	20.3 (42.8)	492	24.7 (47.7)	464
QTc Int / msecs [1]	418.2 (30.7)	493	420.7 (36.8)	467
Sinus rhythm [2]	451 (91.3)	494	460 (93.7)	491
PR >200msecs [2]	68 (13.8)	494	56 (11.4)	491
Mobitz type II heart block [2]	0 (0)	494	0 (0)	491
Wenkebacks heart block [2]	0 (0)	494	0 (0)	491
Bifascicular block [2]	6 (1.2)	494	5 (1.0)	491
Trifascicular block [2]	0 (0)	494	0 (0)	489
Complete heart block [2]	1 (0.2)	494	4 (0.8)	491
Sinus bradycardia <50 [2]	12 (2.4)	494	9 (1.8)	491
Sinus pause >3 seconds [2]	0 (0)	494	0 (0)	490
ST elevation >1mm [2]	16 (3.2)	494	25 (5.1)	491
T wave inversion [2]	278 (56.3)	494	305 (62.1)	491
ST segment depression [2]	30 (6.1)	494	33 (6.8)	487
Pathological Q-waves [2]	120 (24.3)	494	149 (30.4)	490
Pathological Qs not III [2]	72 (14.6)	494	103 (21.0)	490
QTc>450 msecs [2]	71 (14.4)	494	68 (13.9)	490
Left BBB [2]	18 (3.6)	494	21 (4.3)	491
Right BBB [2]	9 (1.8)	494	16 (3.3)	491
QRS ≥120 msecs [2]	27 (5.5)	494	40 (8.1)	491
≥1 ventricular ectopic [2]	34 (6.9)	494	25 (5.1)	487
Atrial tachycardia [2]	11 (2.2)	494	7 (1.4)	491
Narrow complex >100 [2]	30 (6.1)	494	26 (5.3)	491
Broad complex >100 [2]	1 (0.2)	494	2 (0.4)	491

[1] mean (SD), [2] number (%)

Figure 7.2

Graph to show time of attendance for validation followed-up cohort (n=538)



7.4 Outcome measures

Primary outcome:

Of the 538 patients who were available for analysis in the validation cohort [Table 7.3], 39 patients had a serious outcome or all-cause death at one month. Nine patients died.

Secondary outcome:

Of the 9 patients who had died within one month, 8 had a syncope related death. 22 patients had a cardiovascular serious outcome and 16 an obvious diagnosis during ED stay [Table 7.3].

Table 7.3

Summary of validation outcome measures

	Validation Cohort (n=538)
Primary outcome	39
Serious outcome (SO)	35
All cause death (ACD)	9
Both SO & ACD	5
Obvious diagnosis in ED	16
Secondary outcomes	
Cardiovascular serious outcome	22
Syncope related death	8

7.5 Performance of BNP

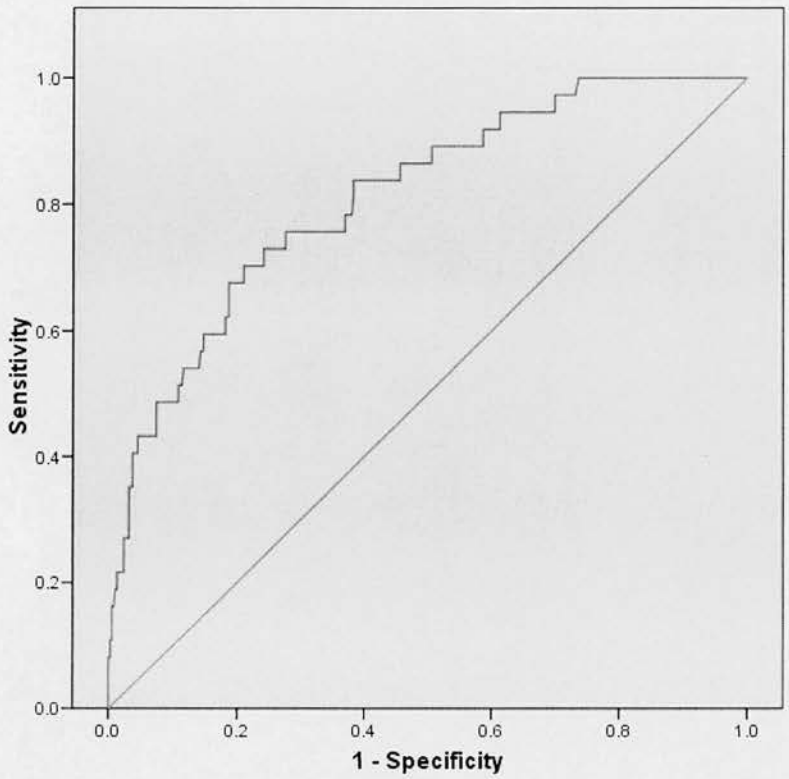
BNP was an excellent predictor of serious outcome or all-cause death in the validation cohort. A BNP concentration ≥300 pg/mL alone predicted 16 (41%) of 39 validation serious outcomes or all-cause deaths, including 8 of 22 (36%) cardiovascular serious outcomes, and 8 of 9 (89%) all-cause deaths missing a patient who died of complications of a hip arthroplasty (99.8% negative predictive value for all-cause death). The area under the receiver operator characteristic (ROC) curve of BNP with serious outcome or all-cause death was 0.81 (95% CI 0.74-0.88). The areas under the ROC curves of BNP with cardiovascular serious outcome and all cause-death were 0.79 (95% CI 0.69-0.88) and 0.93 (95% CI 0.85-1.00) respectively.

Table 7.4 Validation cohort serious outcomes (n=39)

Patient number	Primary outcome (composite endpoint of serious outcome and all-cause death)		Secondary outcomes	
	Serious Outcome?	Death within one month?	Cardiovascular serious outcome?	Syncope related death?
592	AMI	No	Yes	No
597	VT on 24 hr tape	No	Yes	No
623	Severe aortic stenosis requiring aortic valve replacement (AVR)	No	Yes	No
637	Colonoscopy for rectal bleed	No	No	No
638	Pacemaker inserted	No	Yes	No
650	Subarachnoid haemorrhage	No	No	No
675	Bronchoscopy, biopsy secondary to lung carcinoma	No	No	No
681	No serious outcome by definition	Yes - day 3; pneumonia, sepsis, multiple organ failure	No	Yes
698	Cerebrovascular accident (CVA)	Yes - day 6; aspiration pneumonia & CVA	No	Yes
726	Aortic valve repair	No	Yes	No
756	PE	No	No	No
764	AMI	No	Yes	No
779	Endoscopy for upper GI bleed	No	No	No
783	No serious outcome by definition	Yes - day 27; complications of left hemi-arthroplasty	No	No
799	AMI	No	Yes	No
818	Pacemaker inserted	Yes – day 18; out of hospital cardiac arrest	Yes	Yes
828	Pacemaker inserted	No	Yes	No
839	Pacemaker inserted	No	Yes	No
844	AVR and coronary artery bypass graft, AMI	No	Yes	No
851	Angiography after admission with syncope and previous AMI	No	Yes	No
857	Pacemaker inserted for CHB	No	Yes	No
869	Cerebellar infarction	Yes – day 10; cerebellar infarction	No	Yes
871	AMI	No	Yes	No
875	Acute CVA	No	No	No
882	AMI	No	Yes	No
897	Total abdominal hysterectomy for aggressive endometrial CA	No	No	No
903	AMI	No	Yes	No
919	No serious outcome by definition	Yes – day 2; acute renal failure (ARF) & metastatic lung carcinoma	No	Yes
925	CVA and PE	Yes – day 19; CVA/PE	No	Yes
927	Pacemaker inserted for sick sinus syndrome (SSS)	No	Yes	No
929	No serious outcome by def.	Yes – day 29; ARF	No	Yes
933	Left basal ganglia haemorrhage	No	No	No
942	AMI	No	Yes	No
981	VT and 4.5 sec pause on 24hr tape	No	Yes	No
1028	Pacemaker inserted	No	Yes	No
1051	Bradycardia	Yes – day 17; CCF	Yes	Yes
1062	Pacemaker inserted for SSS	No	Yes	No
1067	PE	No	No	No
1087	Upper GI bleed secondary to gastric ulcer	No	No	No

Figure 7.3

ROC curve of BNP versus serious outcome or all-cause death



7.6 Validation study recruitment rate

951 patients presenting between 27th October 2007 and 22nd July 2008 were identified from the EPR search as potentially eligible for inclusion into the validation study. 579 patients were screened for inclusion (60.9%) and 550 were enrolled. 57.8% of patients eligible for inclusion during this validation time period were therefore enrolled into the study.

7.7 Comparison of derivation cohort enrolled patients and derivation cohort eligible but not enrolled patients

Table 7.5 compares enrolled patients and non-enrolled patients in the validation study cohort. There were no significant differences in the mean age, sex ratio, admission or death rates. This suggests that no selection bias was introduced by failing to enrol every eligible patient.

Table 7.5

Comparison of enrolled patients and non-enrolled patients in the validation study cohort.

	Enrolled n=550	Not-enrolled n=401	p
Mean age (SD)	62.1(22.0)	59.2 (24.2)	0.051[a]
Male sex (%)	250 (45.5)	169 (42.1)	0.34[b]
Admitted (%)	287 (52.2)	224 (55.9)	0.29[b]
Discharged (%)	263 (47.8)	177 (44.1)	
Death (%)	10 (1.8)	7 (1.7)	1.00[b]

[a] Students t-test (2-tailed) [b] Chi squared with Yates' continuity correction

Figure 7.4 Age distribution of validation cohort enrolled patients (n=550)

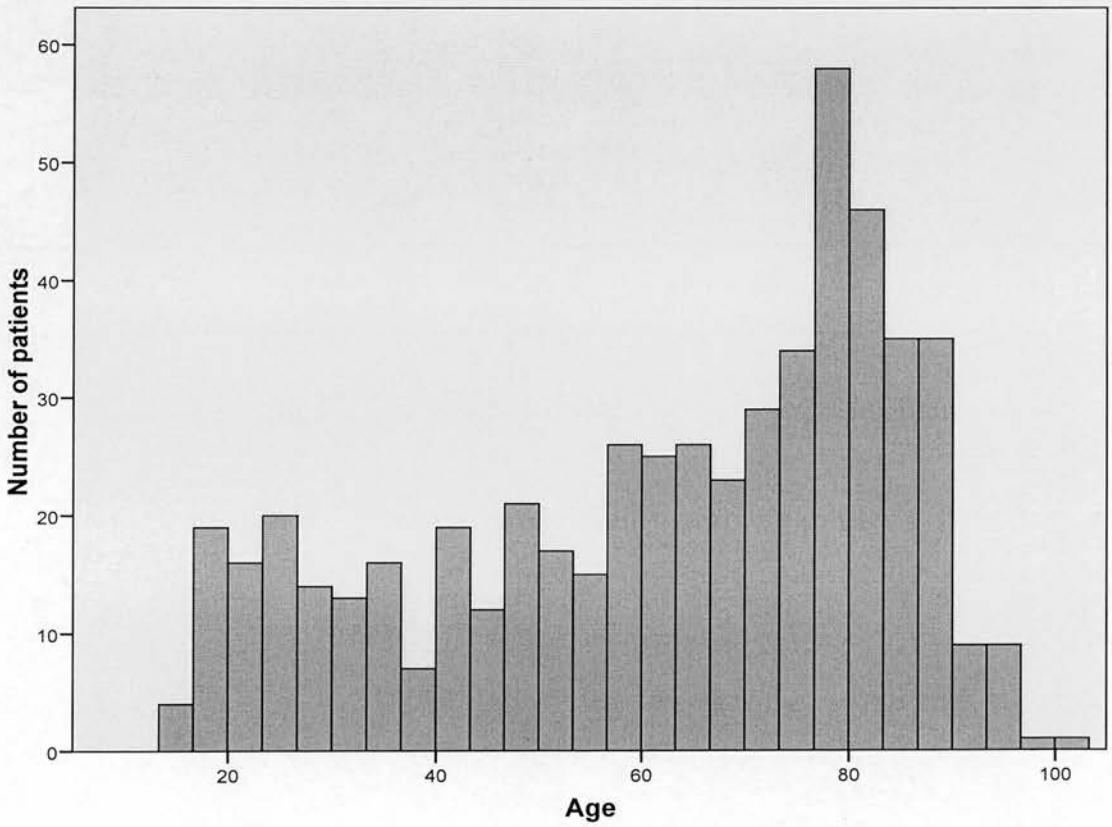
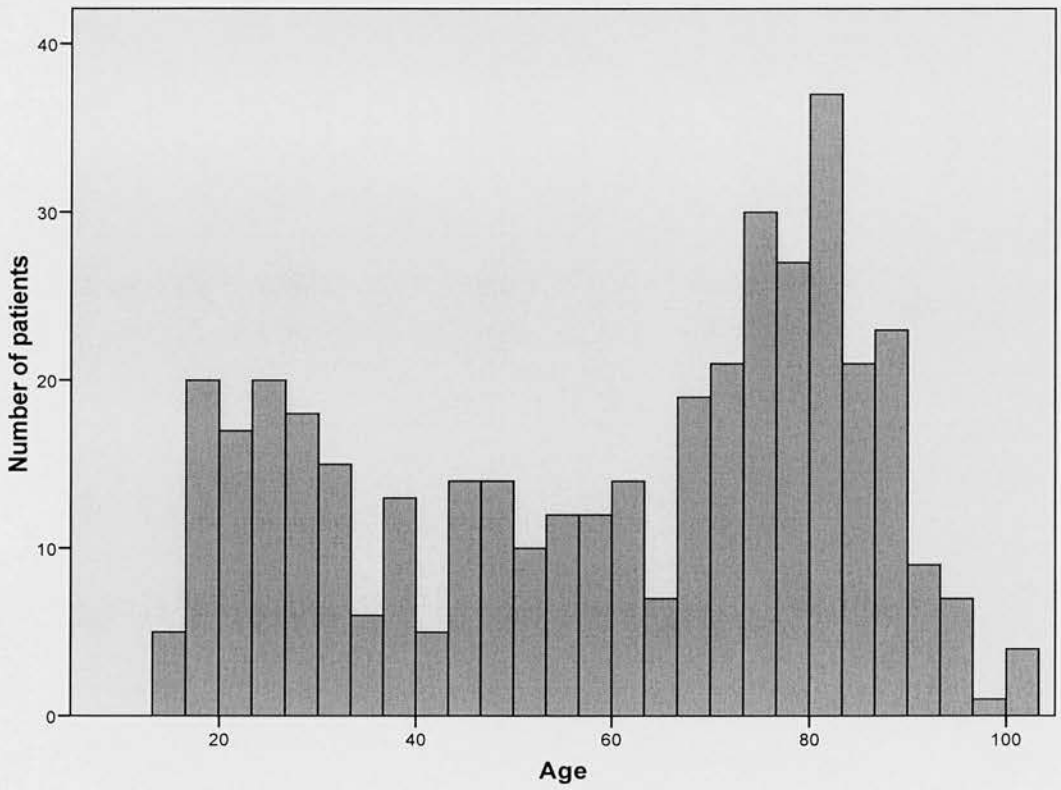


Figure 7.5

Age distribution of validation cohort non-enrolled patients (n=401)



7.8 Interobserver reliability of ECG interpretation

Of the 549 patients participating at baseline data collection in the validation cohort, ECGs were available for 502 with 47 missing. There were no discrepancies in the ECG report between the emergency medicine physician and the cardiologist in 389 of the 502 ECGs (77.5%). Table 7.6 details the validation cohort ECG interobserver agreement.

7.9 Combined interobserver reliability of ECG interpretation

Of the 1097 patients participating at baseline data collection in both cohorts, ECGs were available for 1013 with 84 missing. There were no discrepancies in the ECG report between the Emergency medicine physician and the cardiologist in 862 of the 1013 ECGs (85.1%). Table 7.7 details the combined derivation and validation cohort ECG interobserver agreement.

Table 7.6

Summary of validation ECG interobserver agreement

	Number of positives	Number agreed	Number disagreed	Kappa value (95% CI)	Agreement
Sinus rhythm	469	502	0	1	1
PR >200 msecs	56	501	1	0.99 (0.97-1.0)	0.998
Mobitz type II heart block	0	502	0	1	1
Wenkebach heart block	0	502	0	1	1
Bifascicular block	5	501	1	0.89 (0.67-1.0)	0.998
Trifascicular block	0	502	0	1	1
Complete heart block	4	502	0	1	1
Sinus bradycardia <50	9	502	0	1	1
Sinus pause >3 seconds	0	502	0	1	1
ST elevation >1mm	24	489	13	0.65 (0.48-0.83)	0.974
T wave inversion	313	466	36	0.86 (0.81-0.90)	0.928
ST segment dep >1mm	34	481	21	0.61 (0.46-0.76)	0.958
Pathological Q-waves	150	455	47	0.77 (0.71-0.84)	0.906
QTc > 450 msecs	69	502	0	1	1
Left/Right bundle branch block	37	500	2	0.97 (0.93-1.0)	0.996
QRS duration ≥120 msecs	41	502	0	1	1
Number of vent ectopics	-	497	5	-	0.990
Atrial tachycardia >100	7	502	0	1	1
Narrow complex tachy >100	27	501	1	0.98 (0.94-1.0)	0.998
Broad complex tachy >100	2	502	0	1	1

Table 7.7

Summary of combined derivation and validation ECG interobserver agreement

	Number of positives	Number agreed	Number disagreed	Kappa (95% CI)	Agreement
Sinus rhythm	938	1011	2	0.99 (0.97-1.0)	0.998
PR >200 msecs	124	1011	2	0.99 (0.98-1.0)	0.998
Mobitz type II block	0	1013	0	1	1.000
Wenkebach block	0	1012	1	-	0.999
Bifascicular block	11	1012	1	0.95 (0.86-1.0)	0.999
Trifascicular block	0	1013	0	1	1.000
Complete heart block	5	1013	0	1	1.000
Sinus bradycardia <50	21	1012	1	0.98 (0.93-1.0)	0.999
Sinus pause >3 seconds	0	1013	0	1	1.000
ST elevation >1mm	41	990	23	0.66 (0.54-0.79)	0.977
T wave inversion	600	973	40	0.92 (0.90-0.94)	0.961
ST segment dep >1mm	64	987	26	0.76 (0.67-0.85)	0.974
Pathological Q-waves	271	953	60	0.85 (0.81-0.89)	0.941
QTc > 450 msecs	140	1013	0	1	1.000
Left/Right bundle branch	64	1009	4	0.97 (0.94-1.0)	0.996
QRS duration ≥120 msecs	68	1012	1	0.99 (0.98-1.0)	0.999
Number of vent ectopics	-	1005	8	-	0.992
Atrial tachy >100	18	1013	0	1	1.000
Narrow complex tachy >100	58	1012	1	0.99 (0.97-1.0)	0.999
Broad complex tachy >100	3	1013	0	1	1.000

Electrocardiogram interobserver agreement was between 0.94 and 1.00 for all electrocardiogram variables with kappa values between 0.85 and 1.00 for all variables except ST elevation (0.66; 95% CI 0.54-0.79) and ST depression (0.76; 95% CI 0.67-0.85).

7.10 Interobserver reliability of 'missed' patient interpretation

One month from all derivation and validation recruitment months was randomly selected. Two researchers (MR and KJ) independently reviewed the EPR of all patients presenting to the ED with one of the search terms to decide how many patients were eligible for enrolment.

Table 7.8 details the two researchers interobserver agreement. The agreement was 0.901 with a kappa value of 0.69 (95% CI 0.60-0.77).

Table 7.8

Interobserver agreement of study eligibility between two independent researchers for a randomly selected month.

		Investigator 1 (MR)	
		Eligible	Not eligible
Investigator 2 (KJ)	Eligible	64	15
	Not eligible	28	329

Chapter 8

Results: Performance of the ROSE rule and comparison to existing guidelines

8.1 Performance of the ROSE rule on the validation cohort

The validation cohort database was cleaned and closed prior to analysis and after endpoint determination by an independent clinician blinded to the ROSE CDR (DC). The sensitivity, specificity, positive and negative predictive values and positive and negative likelihood ratios were then calculated for the ROSE CDR in the validation cohort.

The ROSE rule performed with a sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios of 87.2%, 65.5%, 16.5%, 98.5%, 2.5 and 0.2 respectively when applied to the validation cohort missing five patients; raised troponin I and likely AMI, SAH, basal ganglia haemorrhage on day 29, documented episode of ventricular tachycardia in the ED, and a gastric ulcer found on upper gastrointestinal endoscopy. Two of these patients were discharged by the ED clinician (patients with SAH and basal ganglia haemorrhage). Use of the ROSE rule in the validation cohort would have potentially resulted in 80 fewer admissions.

Table 8.1 Use of ROSE rule in validation group

One or more ROSE rule characteristic present?	Serious outcome or all cause death?		Total
	No	Yes	
No	327	5	332
Yes	172	34	206
Total	499	39	538

Table 8.2

Comparison of serious outcomes and admissions in the validation study

Patient admitted?	Serious outcome or all cause death?		Total
	No	Yes	
No	249	3	252
Yes	250	36	286
Total	499	39	538

Table 8.3

Performance of ROSE rule compared to decision to admit in validation cohort

	Current physician performance in validation cohort (i.e. patient admitted)	ROSE rule
Sensitivity % (CI)	92.3 (78-98)	87.2 (72-95)
Specificity % (CI)	49.9 (45-54)	65.5 (61-70)
Positive predictive value % (CI)	12.6 (9-17)	16.5 (12-22)
Negative predictive value % (CI)	98.8 (96-100)	98.5 (96-99)
Positive likelihood ratio (CI)	1.8 (1.6-2.1)	2.5 (2.1-3.0)
Negative likelihood ratio (CI)	0.2 (0.1-0.5)	0.2 (0.1-0.4)

8.2 Comparison to existing clinical decision rules

Figures 1.4, 1.5 and 1.7 detail the three major CDRs that have attempted to predict serious outcome or death in syncope. The performance of the ROSE rule in the validation cohort was compared to the performance of these existing syncope CDRs and also the short-term risk factors from the recently published STePS study [Figure 1.8] in the validation cohort. Table 8.4 summarizes the results. Three other decision rules that were derived to predict arrhythmia or cardiac syncope only were not tested (Oh JH et al, Sarasin FP et al 2003, Del Rosso et al).

Table 8.4 Comparison of ROSE rule to existing CDRs.

	Sensitivity	Specificity	PPV	NPV	+ LR	Area under ROC curve	- LR	Comparison with admission in validation group (n=538)			
								Number extra admitted	Number extra discharged	Number of extra missed serious outcome or death	Number of extra missed deaths
OESIL score >3 [13]: All 4 OESIL criteria present	20.5 (10-37)	92.8 (90-95)	18.2 (9-33)	93.7 (91-96)	2.8 (1.4-5.7)	0.55 (0.45-0.65)	0.9 (0.7-1.0)	-	242	28	6
OESIL score >2 [13]: 3 or 4 OESIL criteria present	69.2 (52-82)	71.9 (68-76)	16.2 (11-23)	96.8 (94-98)	2.5 (1.9-3.2)	0.68 (0.59-0.77)	0.4 (0.3-0.7)	-	119	9	3
ROSE rule: Any criteria for admission present	87.2 (72-95)	65.5 (61-70)	16.5 (12-22)	98.5 (96-99)	2.5 (2.1-3.0)	0.75 (0.68-0.82)	0.2 (0.1-0.4)	-	80	2	0
OESIL score >1 [13]: 2- 4 OESIL criteria present	76.9 (60-88)	41.9 (38-46)	9.4 (7-13)	95.9 (92-98)	1.3 (1.1-1.6)	0.56 0.47-0.65)	0.6 (0.3-1.0)	34	-	6	2
San Francisco syncope rule: Any criteria for admission present [15,16]	84.6 (69-94)	24.4 (21-29)	8.0 (6-11)	95.3 (90-98)	1.1 (1.0-1.3)	0.54 (0.45-0.63)	0.6 (0.3-1.3)	124	-	3	1
Martin GJ et al [11]: One or more criteria present	100 (89-100)	21.6 (18-26)	9.1 (7-12)	100 (96-100)	1.3 (1.2-1.3)	0.57 (0.48-0.66)	0 (n/a)	144	-	0	0
STePS study [17]: Any short-term risk factor present	89.7 (75-97)	19.2 (16-23)	8.0 (6-11)	96.0 (89-99)	1.1 (1.0-1.2)	0.54 (0.44-0.63)	0.5 (0.2-1.4)	152	-	1	0
OESIL score >0 [13]: Any OESIL criteria present	94.9 (81-99)	10.6 (8-14)	7.7 (6-10)	96.4 (86-99)	1.1 (1.0-1.1)	0.52 (0.43-0.62	0.5 (0.1-1.9)	197	-	0	0

Chapter 9

The role of Troponin I

9.1 Introduction and aims

In the 1960s it was believed that cardiac causes, especially AMI, were responsible for most cases of syncope (Williams ER). More contemporary data suggest that cardiac causes account for approximately 10% of all cases of syncope. Most are attributable to arrhythmia or structural cardiopulmonary disease, and less than two per cent are due to AMI (Sarasin FP et al 2001). Cardiac arrhythmias can precipitate syncope if the heart rate is too fast or slow, and unable to maintain cardiac output and systemic blood pressure. Arrhythmias most commonly occur in patients with chronic cardiac, vascular and autonomic disease, and are a frequent complication of AMI. Arrhythmias occur in the majority of AMI patients treated in the coronary care unit, with VT complicating 10-40% and VF 4-18% (Hollander JE). Myocardial ischaemia and infarction, and other structural cardiopulmonary diseases, such as PE and valvular heart disease, can cause syncope through non-arrhythmic mechanisms.

The 1971 World Health Organisation diagnosis of AMI was based on a typical history, characteristic ECG changes and raised cardiac enzymes. In the last decade, troponin, a regulatory protein found in myofibrils, has become the recommended cardiac marker due to its increased specificity and sensitivity for myocyte necrosis. Patients with elevated serum troponin concentrations have an increased risk of death at six months (Fox KAA). In 2007, a combined ESC, ACCF, AHA and WHF task force agreed a universal definition of AMI (Thygesen K et al), which recognises even a small troponin rise in a clinical setting consistent with myocardial ischaemia as an AMI.

Little evidence exists of the incidence of raised troponin in syncope. Because of anxiety about discharging syncope patients without an AMI 'rule-out', it is the practice in many EDs to measure troponin in patients who present with syncope. This widespread practice occurs despite the absence of evidence that measurement of

troponin in patients with syncope in the absence of chest pain has clinical utility in identifying AMI.

Troponin may have a role in the risk stratification of patients with syncope. An elevated serum troponin concentration can occur outwith AMI (Hamm CW et al) and, when present, is associated with an adverse prognosis in many conditions (King DA et al, Rittoo D et al, Ramappa P et al, Giannitsis E et al, Di Angelantonio E et al). Patients with cardiac syncope have a one-year mortality between 10 and 30% (Kapoor WN et al 1983). If a relationship between troponin and serious outcome or all-cause death after syncope is found, it might aid the identification of those people at greatest risk.

The aims of this study were to assess the value of a 12-hour troponin I measurement (1) to identify AMI, and (2) to predict one-month serious outcome or all-cause death in patients presenting with syncope to the ED.

9.2 Methodology

This study used patients enrolled into the ROSE derivation cohort.

9.3 Troponin Measurement

Admitted patients had plasma troponin I concentration measured at least 12 hours after syncope. Discharged patients were invited to return and blood samples were obtained as soon as possible after the incident syncopal episode but no earlier than 12 hours and no later than seven days. Plasma troponin I concentrations were measured using an automated immunoassay (Abbott Architect STAT Troponin-I assay). This assay has a 99th percentile upper reference limit in an apparent healthy population of 0.012 ng/mL and coefficients of variation <10% for all troponin I values ≥0.20 ng/mL. The normal cut-off threshold was therefore taken as a troponin <0.20 ng/mL (Abbott Laboratories Diagnostics Division).

9.4 Endpoint measures

The primary endpoints for this study were admission AMI as defined by the universal definition (Thygesen K et al), and the combination of serious outcome (excluding admission AMI) and all-cause death both at one month after ED presentation.

Because troponin I was used as both a predictor of risk and an endpoint, whilst admission AMI was included as an endpoint for AMI diagnosis prediction, in order to avoid incorporation bias admission AMI was excluded as a serious outcome prior to statistical analysis for risk prediction. Patients who had an admission AMI but who died were included.

Definitions for serious outcome and endpoint review protocol were the same as for the ROSE study and are detailed in chapters 5.8 and 5.9.

9.5 Statistical analysis

Based on an earlier pilot study of 100 patients (see Chapter 4), it was assumed that the study population would have a raised troponin I rate of 10% and that serious outcome or all-cause death would occur in 50% of troponin I-positive patients and 15% of troponin I-negative patients. It was calculated that, to detect a difference in outcome with troponin I measurement, 185 patients with 17 serious outcomes or all-cause deaths would be needed to have 80% power at $p<0.05$.

Statistical analysis (SPSS) was performed using Fisher exact tests and ROC curves. Statistical significance was taken as a two-sided $p<0.05$.

9.6 Results

Between 1st March 2007 and 27th October 2007, 1241 consecutive patients were screened for enrolment into the study [Figure 9.1], 890 were eligible, 289 of which were enrolled and had a plasma troponin I performed [Table 9.1].

Plasma troponin I concentrations were measured in 186 (74%) of the 254 enrolled patients admitted to hospital; 173 of these were normal (<0.2 ng/mL) and 13 were raised [Table 9.2]. Of the 294 enrolled patients who were discharged from the ED, 103 (35%) patients had plasma troponin I concentrations measured at a mean of 42 (SD 53) hours after discharge and only one patient had a troponin I ≥0.2 ng/mL (patient 53=0.21 ng/ml).

Figure 9.1 STROBE diagram of recruited patients.

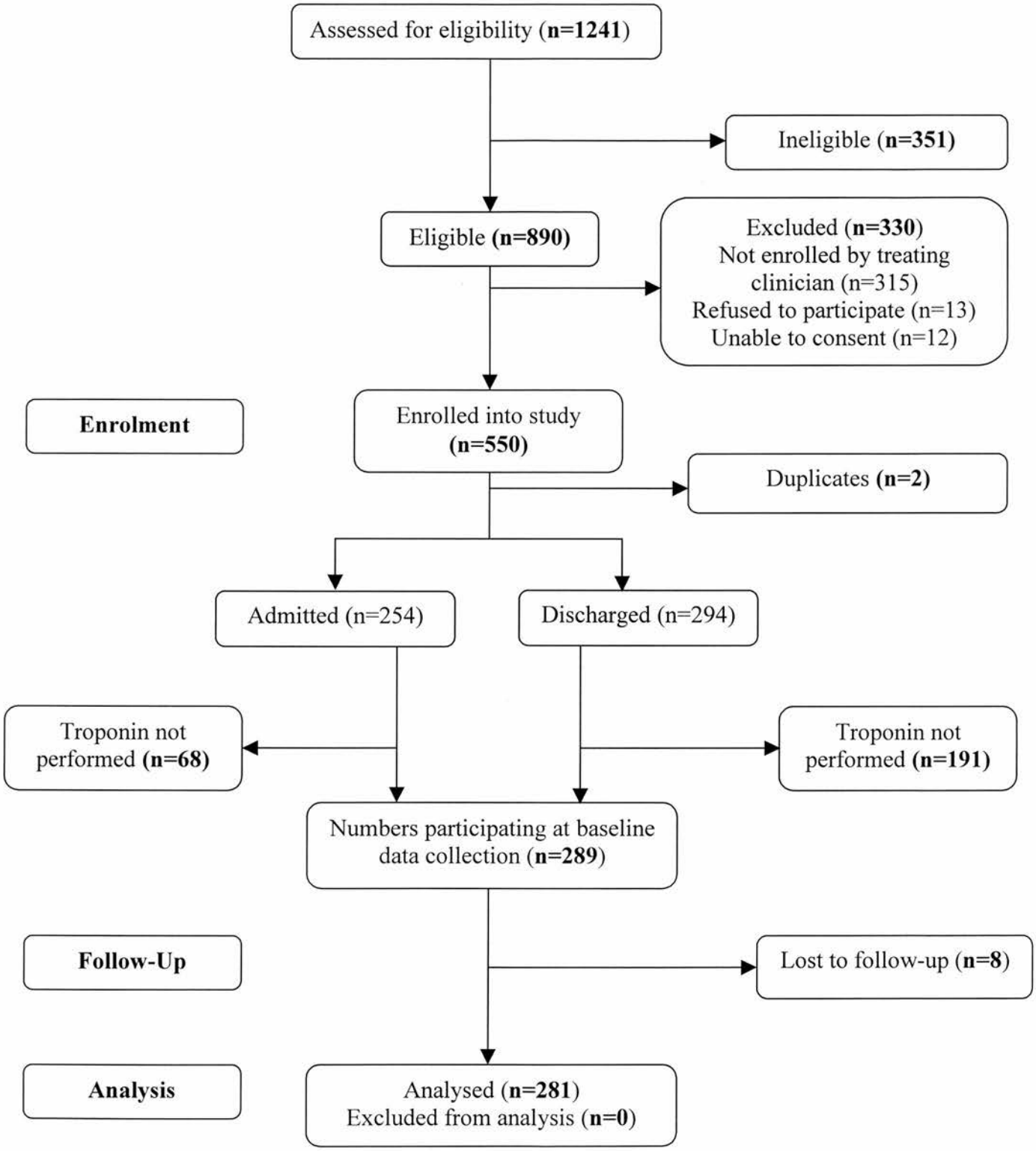


Table 9.1 Characteristics of analysed patients (n=281).

Characteristic	Serious outcome (including admission AMI) or all-cause death (n=25)	Non-serious Outcome (n=256)
Demographics		
Age in years [1]	75.0 (14.7)	67.0 (19.1)
Male sex [2]	14 (56)	126 (49)
Medical history		
Previous history of syncope [2]	10 (40)	115 (45)
>1 episode in previous year [2]	8 (32)	53 (21)
Hypertension [2]	13 (52)	114 (45)
Known ischemic heart disease [2]	14 (56)	76 (30)
Previous AMI [2]	7 (28)	35 (14)
Known valvular heart disease [2]	3 (12)	16 (6)
Previous cardiac arrest [2]	1 (4)	4 (2)
Known history of cardiac failure [2]	5 (20)	18 (7)
Implanted pacemaker [2]	1 (4)	2 (1)
Implanted internal defibrillator [2]	1 (4)	2 (1)
Current medication		
Diuretics [2]	10 (40)	82 (32)
Sublingal GTN or GTN spray [2]	6 (24)	44 (17)
Longer acting nitrates [2]	4 (16)	21 (8)
Calcium channel blocker [2]	7 (28)	40 (16)
Beta blocker [2]	9 (36)	61 (24)
ACE inhibitor / A2 blocker [2]	11 (44)	80 (31)
Nicorandil [2]	2 (8)	7 (3)
Amiodarone [2]	5 (20)	3 (1)
Digoxin [2]	3 (12)	20 (8)
Alpha blockers [2]	0 (0)	12 (5)
Warfarin [2]	6 (24)	14 (5)
Aspririn [2]	12 (48)	81(32)
History of syncope episode		
Associated chest pain [2]	3 (11)	28 (11)
Prodromal symptoms [2]	17 (34)	148 (37)
Associated palpitations [2]	1 (2)	10 (4)
Associated subjective SOB [2]	7 (14)	31 (12)
Associated headache [2]	1 (2)	25 (10)
Associated situational symptoms [2]	1 (2)	17 (7)
Associated with GTN use [2]	1 (2)	10 (4)
Witnessed seizure activity [2]	2 (4)	5 (2)
Related to exertion [2]	4 (8)	14 (5)
Management		
Admitted [2]	23 (92)	162 (63)

[1] mean (SD), [2] number (%)

Table 9.2 Summary of patients with Troponin ≥ 0.2 (n=14).

Study No.	Plasma Troponin I (ng/mL)	AMI?	Serious Outcome?	Death?	Comment
10	0.2	No	Yes	No	Pacemaker insertion for CHB
18	0.35	No	No	No	CRF on dialysis/severe systolic impairment. Died 3 months after episode
53	0.21	No	No	No	Severe dementia discharged from ED
166	0.24	No	No	No	3 day admission - no diagnosis made
228	0.29	No	Yes	No	Pacemaker inserted
233	0.71	No	Yes	No	Episodes of VT on 24 hr tape
242	1.61	No	Yes	No	Documented arrhythmia and death
243	0.25	No	No	No	15 day admission; raised troponin I secondary to new AF
303	33.2	Yes	Yes	Yes	AMI & Death
311	1.09	No	Yes	No	Bilateral PE
369	0.8	Yes	Yes	No	New AF on admission. Chest pain and ischemic ECG later in day due to AMI
404	17.5	Yes	Yes	Yes	AMI & Death
408	1.34	Yes	Yes	No	2-day admission. Post-operative chest pain three days previously at another hospital retrospectively thought to have been AMI
422	0.24	No	No	No	Overnight inpatient stay - no diagnosis made

Four troponin I-positive patients had an AMI according to the 2007 universal definition (Thygesen K et al). None had chest pain, however, all had ECG abnormalities [Table 9.3].

Table 9.3 Presence of chest pain and ECG changes in patients with troponin I ≥ 0.2 (n=14).

Study Number	Associated chest pain?	ST elevation > 1mm?	T wave inversion?	ST segment depression >1mm	Pathological Q-waves?
10	No	No	Yes	No	Yes
18	No	No	Yes	No	No
53	No	No	Yes	No	No
166	No	No	No	No	No
228	No	No	No	No	No
233	No	No	No	No	Yes
242	No	No	Yes	No	Yes
243	No	No	No	No	No
303	No	Yes	Yes	Yes	No
311	Yes	No	Yes	No	No
369	No	No	No	No	Yes
404	No	No	No	Yes	No
408	No	No	Yes	No	Yes
422	No	No ECG	No ECG	No ECG	No ECG

* Grey shading denotes patients diagnosed with AMI.

The presence of ST segment deviation or pathological Q waves had 100% (95% CI 40-100) sensitivity, 72% (95% CI 66-77) specificity and 100% (95% CI 98-100) negative predictive value for the diagnosis of AMI after presentation with syncope [Table 9.4].

Table 9.4 Contingency tables of AMI and the presence of ST deviation or abnormal Q waves (n=289).

		Acute Myocardial Infarction?		Total
		Yes	No	
ST segment deviation or pathological Q waves on presenting ECG?	Yes	4	80	84
	No	0	205	205
Total		4	285	289

Fisher's Exact Test p=0.007

Sensitivity = 100% (95% CI 40-100) Specificity = 72% (95% CI 66-77)
PPV = 5% (95% CI 2-12) NPV = 100% (95% CI 98-100)
Positive likelihood ratio = 3.6 (95% CI 3.0-4.3)

Of the 289 patients in whom a plasma troponin I concentration had been measured, eight were lost to followed-up. None of these eight patients had died or represented to a hospital in the Lothian area. Seven of the 14 patients (50%) with a raised troponin I had a serious outcome (that did not include AMI), or all-cause death [Table 9.5] compared to 16 of the 267 patients (6%) without a raised troponin ($p<0.0001$).

The area under the ROC curve of troponin I versus serious outcome (excluding AMI) or all-cause death was 0.64 (95% CI 0.50-0.78) [Figure 9.2].

Table 9.5 Contingency table of serious outcome (excluding AMI) and all-cause death and troponin I value (n=281).

		Serious outcome (excluding admission AMI) or all-cause death?		Total
		Yes	No	
Troponin I ≥ 0.2?	Yes	7	7	14
	No	16	251	267
Total		23	258	281*

Fisher's Exact Test $p<0.0001$

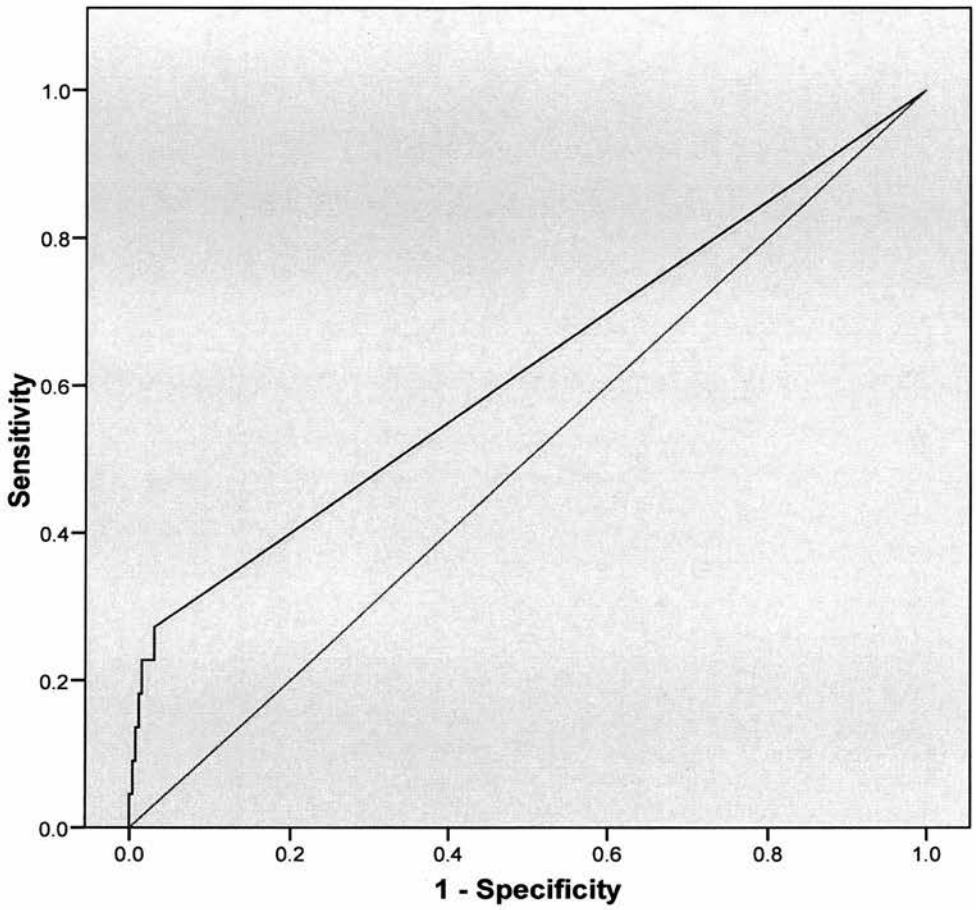
* 8 patients lost to follow -up therefore n=281 rather than 289

Sensitivity = 30% (95% CI 14-53) Specificity = 97% (95% CI 94-98)

PPV = 50% (95% CI 24-76) NPV = 94% (95% CI 90-96)

Positive likelihood ratio = 11.2 (95% CI 4.3-29.2)

Figure 9.2 ROC curve showing relationship between troponin I and serious outcome (excluding initial AMI) or all-cause death in syncope.



9.7 Discussion

It has been demonstrated that AMI is an infrequent (1.4%) cause of isolated syncope presenting to the ED and measurement of plasma troponin I concentrations provides little additional benefit in identifying patients with syncope as a consequence of AMI. Troponin I concentrations do though predict one-month serious outcome or all-cause death, and may assist the identification of those patients who can be safely discharged early after admission.

Three previous studies (Link MS et al, Grossman SA et al, Hing R et al) have looked at the diagnostic yield of troponin to diagnose AMI in patients presenting to the ED with syncope. These studies were predominantly retrospective, and in comparison to the present study, had smaller sample sizes (n=80-141) and lower recruitment rates (22-44%). These studies also reported a low incidence of AMI (1.4-3.5%) although they may have potentially over-estimated the incidence of AMI due to the low rate of troponin estimations in the study populations. This study was prospective, with a relatively high recruitment rate and represents the biggest experience to date. It confirms the earlier findings and extends them by demonstrating that, in the absence of ST deviation or pathological Q waves on the ECG, the diagnostic yield of a troponin I to diagnose AMI in patients presenting with isolated syncope (i.e. no chest pain) is extremely low. This is consistent with the concept that syncope induced by AMI is predominantly driven by life-threatening arrhythmia or major haemodynamic compromise due to profound or widespread ischaemia. These conditions are likely to be associated with marked and readily identifiable ECG abnormalities that will be apparent at presentation.

To meet the new universal criteria for AMI (Thygesen K et al), patients presenting with syncope must have a troponin rise and one of the following: symptoms of ischaemia, ECG changes, or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. Syncope in itself is not a specific symptom of ischaemia. Therefore, in the absence of a history consistent with myocardial ischaemia or ECG changes, it is extremely unlikely that patients with syncope will be diagnosed with AMI in the ED.

Troponin has been associated with an adverse prognosis in many condition (King DA et al, Rittoo D et al, Ramappa P et al, Giannitsis E et al, Di Angelantonio E et al), some of which are known to cause syncope. In acute PE, troponin release occurs secondary to acute systemic haemodynamic compromise and right heart pressure overload. The haemodynamic compromise and intense sympathetic nervous system discharge may also underlie the elevation in plasma troponin concentrations associated with conditions such as SAH and type A aortic dissection (Bonnefoy E et al). It would therefore seem likely that troponin release following syncope is a marker of adverse haemodynamic compromise and a serious underlying cause is likely. This underlines the wider prognostic importance of troponin elevation and may assist in risk stratification of patients presenting with syncope.

In this study, only 74% of patients admitted to hospital had a troponin I measured. This may reflect case selection bias by the attending clinician. Although there was no sex bias ($p=0.394$), mean age was higher in those who had a troponin measured (74 ± 14 versus 68 ± 18 years, $p=0.018$). This suggests that the attending physician was more likely to measure plasma troponin in older patients, perhaps reflecting concern of excluding silent AMI as a cause of syncope. However, there were 23 serious outcomes or all-cause deaths in the 185 patients who had a troponin I estimation (12%), and 12 serious outcomes or all-cause deaths in the 67 who did not have a level estimated (18%; $p=0.303$). Assuming troponin was more likely to be measured in those perceived to be at high risk, this would suggest that the clinician was unable to identify high risk patients reliably.

9.8 Study Limitations

This was a prospective cohort observational study that assessed the apparent clinical utility of troponin measurement in patients presenting with syncope. A more robust approach would have been to measure plasma troponin I concentrations in all patients to get full case ascertainment and a more robust prediction of risk. This data would suggest that this is particularly applicable to those patients hospitalised following syncope.

Troponin I was used as both a predictor of risk and an endpoint (AMI) which could lead to incorporation bias. This problem was adjusted for by excluding admission AMI as a serious outcome prior to statistical analysis for risk prediction.

Chapter 10

The role of D-Dimer

10.1 Introduction and Aims

D-dimer is a degradation product of cross-linked fibrin released after fibrinolysis, which has long been identified as an independent marker of PE. A plasma D-dimer concentration in the normal reference range has a 95% negative predictive value for excluding PE (Haslett C et al). The BTS guidelines state that a negative D-dimer test will reliably exclude PE in patients with low or intermediate clinical risk (BTS Guidelines). While a high plasma concentration does not confirm diagnosis, it is recognised to have useful predictive value in terms of PE prognosis and response to treatment (Altiay G et al).

Anecdotally there are patients who present with syncope as the only presenting symptom of PE. One might expect that a PE large enough to cause haemodynamic compromise and syncope would be detectable on clinical history and examination without the need for D-dimer estimation. The incidence of a raised D-dimer in syncope patients is unknown.

Recent studies have shown the usefulness of D-dimer as an independent marker of coronary artery disease in patients with stable angina, but have found no association between extent and severity (Koenig W et al). Raised plasma D-dimer concentrations are an independent risk factor for future coronary events in healthy subjects of both sexes (Koenig W et al, Lowe GDO et al). The Edinburgh Artery study looked at 17 different biochemical blood markers including D-dimer. Baseline plasma concentrations were consistently higher in patients who subsequently developed coronary artery disease. Patients with cardiac syncope have one-year mortality between 10 and 30%. If a relationship between D-dimer and cardiovascular serious outcome after syncope is found, it might aid identifying those people at greatest risk.

It was hypothesised that D-dimer estimation would aid the identification of high-risk syncope patients in the ED. The primary aim of this study is to establish whether D-dimer is an independent predictor of one-month serious outcome and all-cause death in syncope patients presenting to the ED. Secondary aims are to determine (1) the incidence of a raised D-dimer in syncope patients and (2) whether D-dimer predicts one-month serious cardiovascular outcome.

10.2 Methodology

This study used patients enrolled into the ROSE derivation cohort. All patients presenting with syncope who had a three millilitre citrated blood sample (Monovette; Sarstedt Incorporated) taken at presentation were eligible for inclusion. Patients were assessed clinically using a predefined DCF. The citrated blood samples were spun, separated and refrigerated before being frozen to -20°C within 24 hours. All samples were analysed as a single batch using an automated ACL TOP coagulation analyser in the hospital clinical haematology laboratory. The ACL TOP analyser uses the HemosIL DD HS (Instrumentation Laboratory, Lexington, MA, US) assay, which is a new microparticle-enhanced turbidimetric immunoassay. The assay has a reported sensitivity for detection of venous thromboembolism of 100% with intra and interassay CVs of ~7% (de Moerloose P et al).

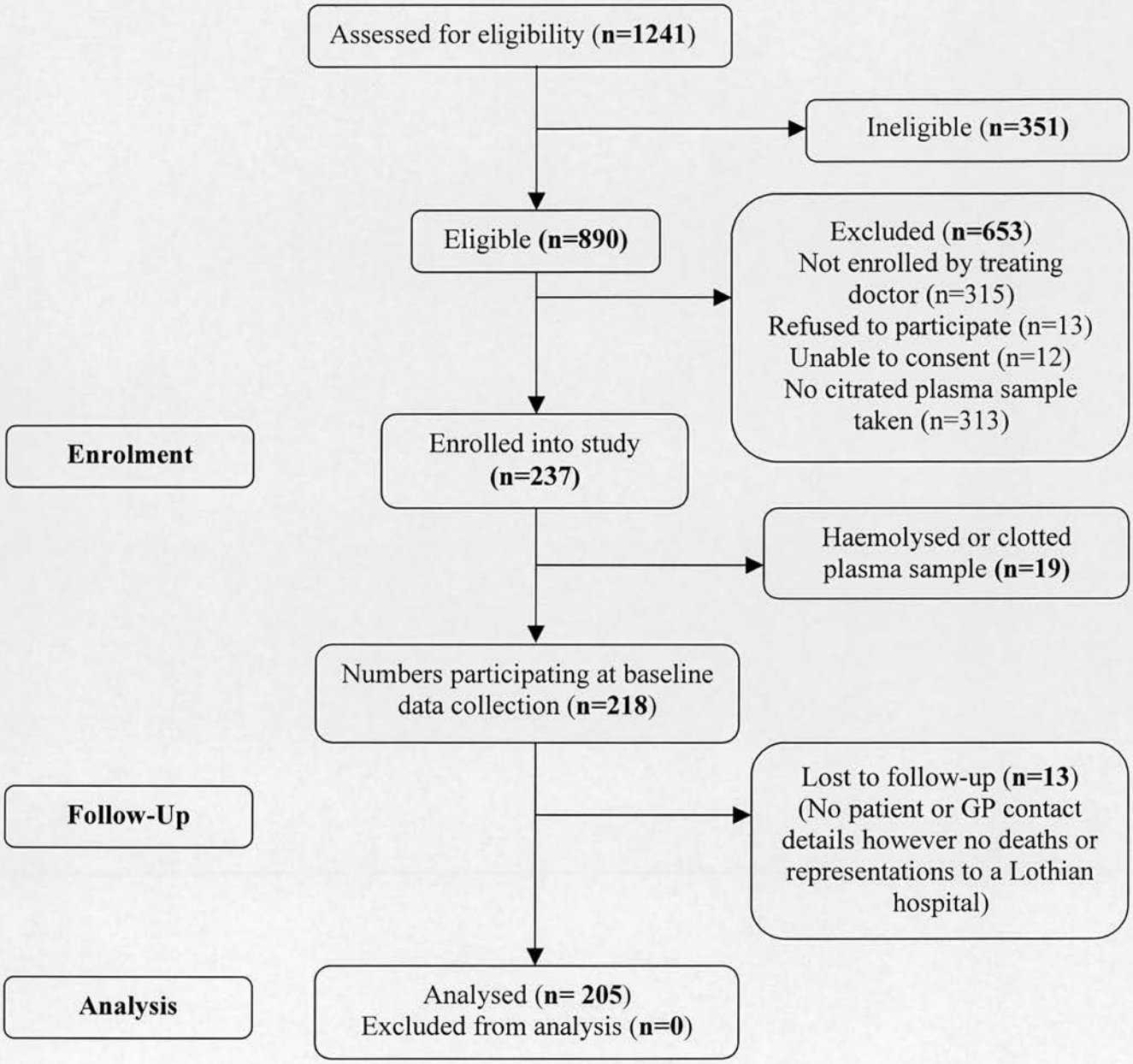
The primary endpoint for this study was the combination of serious outcomes and all-cause death at one month after ED presentation. The secondary endpoints were cardiovascular-related serious outcome and PE at one month after ED presentation. Cardiovascular serious outcome was defined as AMI, life-threatening arrhythmia or insertion of pacemaker or internal cardiac defibrillator device within one month of the ED attendance or subsequent insertion related to index collapse.
Definitions for serious outcome and endpoint review protocol were the same as for the ROSE study and are detailed in chapters 5.8 and 5.9.

Patients presenting during the study period were identified from a search of all EPRs as potentially eligible for inclusion into the study. Statistical analysis using SPSS involved calculation of median values, inter-quartile ranges and construction of ROC curves.

10.3 Results

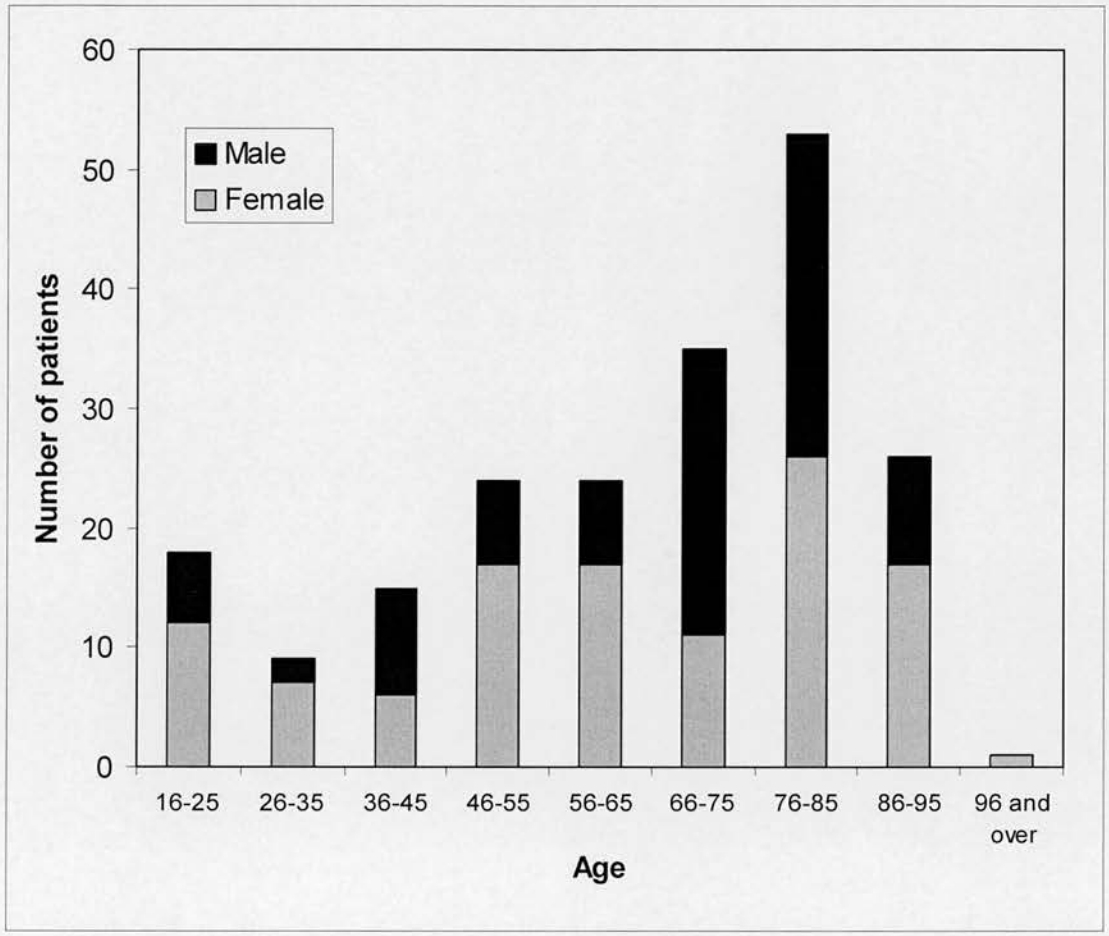
From 1st March to 27th October 2007, 890 patients presented to the ED and were potentially eligible for inclusion into the study. 237 patients were enrolled into the study (26%) and had at least one citrated blood sample taken. There were 249 citrated samples available from 237 patients. Where two samples were available, both samples were assayed and the lower result was used in the subsequent analysis. After removal of unsuitable and duplicate samples there were 218 D-dimer results available for analysis. Although full follow-up was not available for 13 patients, it was possible to ascertain that none of these patients had died or represented to a Lothian hospital. This left a final study population of 205 [Figure 10.1].

Figure 10.1 STROBE diagram of recruited patients.



The study population was elderly (mean 64.3 years; SD 21.2) and predominantly female (n=114; 56%) (Figure 10.2).

Figure 10.2 Age and sex distribution of analysed patients (n=205).



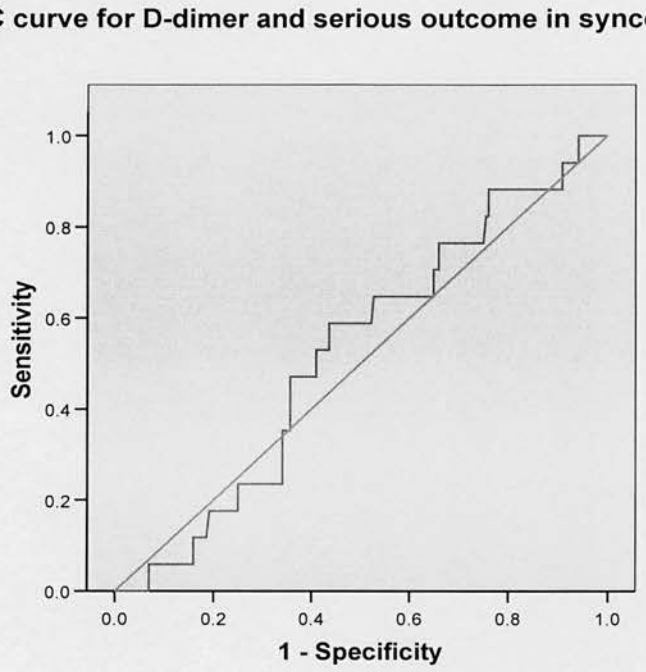
99 patients were hospitalised (48%) of whom 47 were female (47%). Of the 205 patients, 17 had a serious outcome or death at one month [Table 10.1]. Three patients had a PE and eight had other serious cardiovascular outcomes.

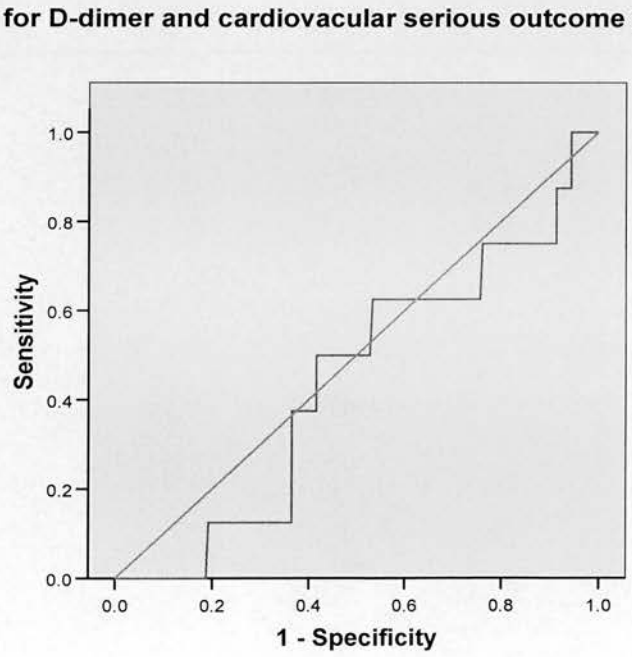
111 patients (54%) had a plasma D-dimer concentration below 500 ng/mL (upper limit of normal reference range). Of the 94 patients with a D-dimer concentration above 500 ng/mL (46%), 10 had a serious outcome or death. The median D-dimer concentration was 450 ng/mL (IQR of 226-725 ng/mL). D-dimer was not a good predictor of serious outcome or death nor of serious cardiovascular outcomes [Figure 10.3].

Table 10.1 Patients with serious outcome or death at one month.

Patient number	Serious Outcome	Cardiovascular serious outcome?
23	Died - Death certificate: 1a MI, 1b Ischemic heart disease, 2 Chronic obstructive pulmonary disease	YES
84	Required colonoscopy and transfusion	NO
100	Permanent pacemaker insertion	YES
124	Died - Death certificate: 1a pneumonia 1b Non-small cell lung carcinoma	NO
125	Automated Internal Cardiac Defibrillator (AICD) delivered appropriate shock for episode of VF	YES
155	Permanent pacemaker insertion for CHB	YES
158	Transfusion for GI bleed	NO
189	Transfused two units for Mallory Weiss tear	NO
193	Endoscopic procedure	NO
209	AICD delivered appropriate shock for episode of VT	YES
233	Episodes of VT on 24 hr tape	YES
295	PE diagnosed 19 days later	NO
300	Two units blood transfusion for melaena	NO
303	AMI and subsequent death	YES
311	Bilateral PE	NO
375	Temporary pacing wire place for episode of asystole	YES
488	PE	NO

Figure 10.3 ROC curves showing relationship between D-dimer and serious outcome or death in syncope, and relationship between D-dimer and cardiovascular outcome in syncope.





10.4 Discussion

This is the first study to define the incidence of an elevated plasma D-dimer concentration in patients presenting with syncope to the ED. The high frequency (44%) of raised D-dimer concentrations was surprising. The elevation of this marker in nearly a half of patients markedly limits its ability to identify those patients who will be at high-risk of serious outcome. Indeed, based on these findings, it was concluded that routine plasma D-dimer estimation has no role in the prediction of adverse outcome and risk stratification of such patients in the ED. One putative theory for the high frequency of raised D-dimer is that syncope patients may have an increased likelihood of soft tissue injury or bruising as a consequence of their collapse which may in turn lead to a raised D-dimer. There is no evidence however in the literature to support this idea.

Syncope is a common cause of ED attendance and remains a major cause for acute health care resource utilisation. It is associated with both serious clinical outcome and unnecessary hospitalisation. There remains a need for better risk stratification and identification of patients at risk of early adverse events. Plasma D-dimer concentration has little if any utility in either the diagnosis or risk stratification of such patients. Whilst clinical and ECG assessment remain the current mainstay for the diagnosis and risk stratification of patients with syncope (Colivicchi Fet al, Martin TP et al, Quinn JV et al 2004, Quinn JV et al 2006), there are several potential novel biomarkers of risk that are currently under evaluation for a range of acute medical conditions. These include N-terminal pro-brain natriuretic peptide, C-reactive protein, myoglobin and ischemia-modified albumin (Doust JA et al 2005, Alonso-Martinez JL et al, McCord J et al, Kontos M, et al). Whilst none has yet been prospectively evaluated in patients with syncope, some, such as ischemia-modified albumin, lack specificity (Keating L et al) and may also have a high incidence in this patient population with a corresponding lack of discriminatory power. Future work should be targeted at evaluating other potential biomarkers to better aid diagnosis and predict early outcome.

The measurement of plasma D-dimer concentrations has an established role in patients with suspected PE with an excellent negative predictive value of 95%

(Haslett C et al). Whilst the study patients were not being assessed for suspected PE, the latter is a recognised cause of syncope. Of the three patients in this study who were diagnosed with a PE (1.5%), only one was picked up initially through the ED history and clinical examination. The other two patients were not diagnosed until later in their hospital stay. In this cohort, an elevated plasma D-dimer concentration had a positive predictive value of only 3% (3/94) and a very poor specificity of 55% (111/202) for detecting PE in patients with syncope. Whilst PE should be considered as a possible diagnosis in patients with syncope, the routine measurement of D-dimer to diagnose PE in patients presenting with syncope is not appropriate.

One limitation of this study was that only 26% of eligible ED patients were enrolled. There is no reason to believe that the patients who had a citrated blood sample taken for later analysis were not representative of the whole population of ED syncope patients, sampling bias may have occurred. If the treating physician felt that a patient was more or less likely to have a diagnosis of PE or another cardiovascular condition, this may have altered their likelihood to obtain or store a citrated sample for later analysis.

Chapter 11

Final discussion, suggestions for future work and conclusions

11.1 Discussion

The ROSE rule consists of seven variables, which can be easily remembered via the mnemonic BRACES.

Figure 11.1 The ROSE Rule

The ROSE rule	
Admit if <u>any</u> of the following are present:	
B	B NP level ≥ 300pg/ml
	B radycardia ≤50 in Emergency Department or pre-hospital
R	R ectal examination showing faecal occult blood (if indicated)
A	A naemia - Haemoglobin ≤90 g/l
C	C hest pain associated with syncope
E	E CG showing Q wave (not in lead III)
S	S aturation ≤94% on room air

A patient should be considered high risk for serious outcome and admitted if any one of the seven characteristics is present.

It performs considerably better than previous CDRs [Table 9.4] avoiding 149 unnecessary admissions at the expense of missing 4 more patients with a serious outcome, and no deaths for every 1,000 patients presenting with syncope. If incorporated into clinical practice it could potentially save 70,000 admissions and £91 million annually in the UK alone (UK HRG tariffs).

This is the first study to use near-patient BNP as a novel predictor of outcome in patients presenting with syncope. Increasingly, BNP is being recognised as a marker of future risk and death in a range of cardiovascular disease states and not just heart failure. These observations have been extended to a broad group of patients

presenting with syncope, and have demonstrated that it is the single most powerful predictor of adverse outcome and particularly death. Whilst only 5% of UK EDs currently have near-patient BNP testing (Stockley CJ et al), 44% have near patient testing facilities and because of NICE recommendations (NICE 2003), almost all have rapid access to laboratory BNP, which correlates well with near-patient measurement. The utility of BNP is likely to reflect the fact that it is a more objective marker of heart disease than a subjective clinical history or examination.

The RIE ED previously used guidelines (Reed MJ et al 2007a), based on international syncope guidelines (Linzer M et al 1997a, Linzer M et al 1997b, Molzen GW et al, Brignole M et al 2004, Brignole M et al 2001) in an attempt to ensure all high-risk syncope patients were admitted. Such guidelines were impractical, cumbersome, non-specific and led to needless admissions. The perfect CDR would identify all serious pathologies for admission and all low-risk patients for discharge. Such a rule would be too complex and not clinically useful. When compared to other CDRs, no other rule saves admissions without a huge and unacceptable increase in missed serious outcomes. The only two rules which do not miss serious outcomes required admission of 268 and 366 extra patients per 1,000 patients, and include admission criteria such as 'age over 45'.

This study and other recent studies suggest that risk of serious outcome is now much less than previously thought with 1.5% combined one-month mortality in this cohort, 0.7% seven day mortality in the SFSR derivation cohort (Quinn JV et al 2004), 0.4% 30-day mortality in the SFSR validation cohort (Quinn JV et al 2006) and 9.9% combined one-year mortality in the OESIL cohorts (Colivicchi F et al). This compares to 14% and 14.5% one-year mortality in older studies (Kapoor WN & Martin TP et al), suggesting that either syncope may be a more benign condition than previously thought or that more likely, physicians are now better at identifying high-risk patients. It may be that the majority of patients therefore do not require admission.

Patients not enrolled into the derivation cohort were significantly younger, but had a trend towards admission and also a trend towards being more likely to die. This is strange at first glance but probably results from a combination of two factors. Firstly, the treating clinician may have been less likely to enrol young patients with simple

neurocardiogenic syncope due to a perceived view that the study was mainly concerned with patients whose management was unclear. Secondly, the treating clinician may have also been less likely to enrol patients who were extremely unwell because of time pressure and consent/assent issues. These patients would be more likely to require admission and to die.

It was decided to have two 'experts' to review the ECGs; a registrar in cardiology and a consultant emergency physician, rather than the more pragmatic approach of asking the treating clinician to interpret the ECG. Whilst this ensured that ECG analysis was accurate, it must be remembered that treating clinicians are commonly more junior meaning that in practice ECG interpretation may be prone to error.

The ROSE rule is easy to recall and use, and all components are available shortly after presentation. It may be able to aid the emergency physician, the general or acute physician and the general practitioner to determine those patients whose need for admission is unclear. Clearly prior to incorporation into clinical practice in these settings, it will need to undergo external validation in each.

This study has several limitations. As yet it has only been derived and validated in a single UK centre. Recruitment into an external validation study is currently ongoing. Until external validation is successfully performed the rule cannot be adopted into routine clinical practice.

Secondly, whilst saving 149 unnecessary admissions per 1,000 patients with no extra deaths, the ROSE rule misses 4 more patients with serious outcome. Due to the strict definition of serious outcome chosen, most of these are not life-threatening and the clinical benefit of a large number of saved admissions far outweighs the small number of missed potentially serious outcomes.

Finally, the CDR was derived using undifferentiated syncope attendances rather than those with no clear diagnosis after initial evaluation. It was felt that definition of an 'obvious' diagnosis differs widely between individual clinicians and only 42% (33/79) of subsequent serious outcomes and deaths were apparent in the ED. Clearly a CDR is not required when serious pathology is immediately apparent in the ED and

any CDR should only be used in conjunction with physician judgement and not in patients with obvious serious pathology. The ROSE rule identified 85% (39/46) of patients in both cohorts whose subsequent serious outcome or death was not apparent in the ED.

The ROSE rule has been derived and validated. It has excellent sensitivity, specificity and negative predictive values which allows the identification of high-risk syncope patients. The rule potentially reduces admission rates by 30% and is intuitively sensible as different components target different pathologies. The ROSE rule may prove to be very useful when combined with physician judgement. Clearly, external validation is required. Recruitment into such an external validation study is currently ongoing.

11.2 Suggestions for further work

Three steps are involved in the development and testing of a CDR. Firstly the rule must be created or derived. Secondly it must be tested or validated, and finally the impact of the rule on clinical behaviour must be assessed (McGinn TG et al). The ROSE CDR has been successfully validated, however part of the validation process should also involve external validation in a new clinical setting. Once this has been successfully done the CDR can be considered to be a level 1 CDR and appropriate for implementation (McGinn TG et al). External validation of the ROSE rule is currently underway in London, however ideally multicentre validation or several external validation studies in multiple clinical settings with differing incidences of disease should be done prior to implementation of the rule. Previous CDRs have failed to externally validate well (Quinn et al 2006). Whilst it may be that the same fate befalls the ROSE rule, the study's rigorous methodology and use of numerous derivation characteristics suggests it will validate well in a UK population. Further studies would be required to assess its utility in an international setting.

If the rule is found to successfully externally validate then an assessment of how the CDR impacts on clinician behaviour should also be performed. This has been termed impact analysis, and attempts to show that use of the CDR changes physician behaviour and/or improves patient's outcomes and/or reduces costs. In an ideal world,

an impact study would involve randomising patients to either the application or non-application of the CDR. Patients would be followed-up to look at quality of life, morbidity, and resource utilization. This method is unlikely to be appropriate as one would expect the participating clinicians to incorporate the CDR into the care of all their patients and not just the ones who have been randomised to use of the CDR. A good alternative is to randomise institutions or to look at a group before and after clinicians began to use the CDR and compare that with a control group in which there has been no intervention.

After successful external validation, it is planned to assess impact analysis by randomising six UK EDs to either use the ROSE rule or not. The physicians at the intervention institutions would be educated in the CDR, pocket cards, posters and other aide memoires would be distributed and DCFs would be collected specific to the ROSE rule variables and compared to practice in the control EDs.

It is also planned to assess the utility of the ROSE rule within a clinical decision unit once the RIE ED observation unit opens. Patients who have one of the seven ROSE high-risk characteristics could undergo echocardiography, 4-6 hour ECG telemetry and other focussed investigations to enable further risk stratification into those who may be able to be discharged home safely after a short period of observation, and those who would benefit from a further period of inpatient observation and investigation. Funding application for these further studies is currently in progress.

In this study, BNP seems to successfully predict patients at risk of mortality and also cardiovascular morbidity. It may be beneficial to further study this marker in other disease categories to determine how BNP can be best used in the ED and to what group of patients it is most specific.

Finally, ethical approval has been granted to follow-up this cohort of patients at one year. Whilst this has already been done in other cohorts, none have been UK based. This will enable assessment of the longer term morbidity and mortality associated with syncope in our population. The utility of the ROSE rule for long-term (one-year) outcome will also be assessed.

11.3 Conclusions

A UK CDR has been developed and validated to predict one-month serious outcome and all-cause death in patients presenting with syncope to the ED. The rule has excellent sensitivity and negative predictive value and may be a valuable rule to help risk stratify ED syncope patients.

AMI is infrequent (1.4%) in patients with isolated syncope (i.e. no chest pain) and estimation of troponin I provides little additional benefit to the ECG in identifying patients with syncope due to AMI. Troponin I should not used to rule out AMI in adult patients presenting with isolated syncope. Troponin I may predict one-month serious outcome or all-cause death in patients presenting with syncope to the ED.

Plasma D-dimer is frequently raised in patients presenting with syncope to the ED and consequently does not predict one-month serious outcome or death. There is no role for the routine measurement of D-dimer in the management of patients presenting to the ED with syncope.

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Appendices

Appendix 1 Data Collection Form

Risk stratification Of Syncope
in the Emergency department

The ROSE study

ROSE main data collection form part A **Page 1**

Patient details

(Please attach A&E sticker here)

Enrolling doctor details:

Name:_____

Is patient eligible to be enrolled in the ROSE study?

Is the patient over the age of 15?	Yes ☐	No ☐
Have they had an episode of syncope?	Yes ☐	No ☐
Can the patient give informed verbal or written consent **or** is a relative or guardian present who can give written assent?	Yes ☐	No ☐
Does the patient have a good history of a seizure with a definite prolonged post-ictal phase?	Yes ☐	No ☐
Is the patient's collapse suspected to be due entirely to excessive alcohol consumption?	Yes ☐	No ☐
Has the patient already been enrolled to the Main ROSE Study after 1st March 2007?	Yes ☐	No ☐

If all of the shaded boxes are ticked then the patient is eligible.

IF YES: Please give the patient a Patient Information Sheet and ask them to complete the Patient Consent Form on Page 3, **or** their relative or guardian to complete the Relative's Consent Form on Page 4. Please then complete pages 5 and 6 and attach a copy of the patient's ECG to page 7. Take bloods using the study stickers on page 8 and perform a near patient BNP using the meter. On completion, place the form in the ROSE study form collection box, thank you.

IF NO: If the patient is not eligible please place the form complete with patient sticker in the ROSE study form collection box, thank you.

REASON INELIGIBLE: _____

PATIENT CONSENT FORM

(See page 159)

RELATIVE / GUARDIAN CONSENT FORM

(See page 161)

History of syncopal episode

Prodromal symptoms?	Yes ☐	No ☐
Palpitations prior to syncope?	Yes ☐	No ☐
Associated chest pain?	Yes ☐	No ☐
Subjective SOB?	Yes ☐	No ☐
Associated headache?	Yes ☐	No ☐
Situational symptoms i.e. micturation?	Yes ☐	No ☐
Related to GTN use?	Yes ☐	No ☐
Related to exertion?	Yes ☐	No ☐
Witnessed seizure activity?	Yes ☐	No ☐

Past Medical History

Previous episodes of syncope?	Yes ☐	No ☐
>1 episode in the last year?	Yes ☐	No ☐
Previous hypertension?	Yes ☐	No ☐
Known ischemic heart disease?	Yes ☐	No ☐
Previous myocardial infarct?	Yes ☐	No ☐
Known history of valvular heart disease?	Yes ☐	No ☐
Previous history of cardiac arrest?	Yes ☐	No ☐
Known history of cardiac failure?	Yes ☐	No ☐
Pacemaker?	Yes ☐	No ☐
Implantable defibrillator?	Yes ☐	No ☐

Drug History – Is the patient currently taking.....

Diuretics?	Yes ☐	No ☐
Sublingual GTN or GTN spray?	Yes ☐	No ☐
Longer acting nitrates?	Yes ☐	No ☐
Ca^{2+} Channel blockers?	Yes ☐	No ☐
Beta Blockers?	Yes ☐	No ☐
ACE inhibitors / A_2 blockers?	Yes ☐	No ☐
Nicorandil?	Yes ☐	No ☐
Amiodarone?	Yes ☐	No ☐
Digoxin?	Yes ☐	No ☐
Other anti-arrhythmic?	Yes ☐	No ☐
If yes, which one? _____		
Alpha blockers?	Yes ☐	No ☐
Warfarin?	Yes ☐	No ☐
Aspirin?	Yes ☐	No ☐

Examination

Pulse: ☐☐☐

Temperature: ☐☐.☐ °C

Initial BP: ☐☐☐ / ☐☐☐ mmHg

Postural drop (>20 mmHg on standing)? Yes ☐ No ☐

Not performed ☐

Systolic difference if present: ☐☐ mmHg

Oxygen saturation on room air: ☐☐☐ %

Blood Sugar: ☐☐.☐ mmol

Initial GCS: ☐☐

Heart murmur heard? Yes ☐ No ☐

Clinical signs of heart failure present? Yes ☐ No ☐

New neurological signs on examination? Yes ☐ No ☐

FOB +ve on PR? Yes ☐ No ☐

Melena on PR? Yes ☐ No ☐

PR not performed ☐

Trauma associated with collapse? Yes ☐ No ☐

If so what?_____

_____

Point of Care BNP test: Result ☐☐☐☐☐.☐ pg/ml

Reason for omission if not performed? _____

Cause of syncope identified in ED? Yes ☐ No ☐

If so what?_____

Patient discharged from the ED? Yes ☐ No ☐

Referred to MOPD? Yes ☐ No ☐

Patient admitted to RIE? Yes ☐ No ☐

Please attach a copy of patient's initial ECG here

Study Laboratory Request Form

Enrolling doctor checklist

1. Patient eligible and page 2 completed? Yes ☐ No ☐
2. Patient written consent obtained and recorded on page 3? Yes ☐ No ☐
   or patient verbal consent obtained and recorded on page 3? Yes ☐ No ☐
   or relative/welfare guardian written consent obtained and recorded on p.4? Yes ☐ No ☐
   or consent refused Yes ☐ No ☐
3. Patient given Patient Information Sheet from box in HD area? Yes ☐ No ☐
4. History and exam findings recorded on pages 5&6? Yes ☐ No ☐
5. Copy of ECG attached to page 7? Yes ☐ No ☐
6. 2 x red, 1 x yellow, 1 x orange and 1 x green blood tube taken and labelled with normal A&E patient sticker? Yes ☐ No ☐
7. BNP test performed in A&E using one of red tubes and result recorded on p.6? Yes ☐ No ☐
8. Other blood tubes sent to labs using form on page 8? Yes ☐ No ☐
9. If patient **admitted**, 12 hr troponin requested on typed notes? Yes ☐ No ☐
   Not admitted ☐
10. If patient **discharged**, Troponin clinic booked within 7 days?

    Yes, patient agreeable and Troponin clinic booked ☐

    No, patient not agreeable to return to Troponin clinic ☐

    If patient not agreeable to come back please still include in study

    Patient admitted ☐
11. This form to be filed in box in HD area, thanks Matt

Thank you for enrolling the patient and completing the study form.

Please make sure that you have done a near-patient BNP test and have requested the study bloods using a study lab form.

Study bloods = Full blood count, urea, creatinine, LFTs, glucose, electrolytes, Ca^{2+}, Mg^{2+}, PO^{4-}, high sensitive CRP = 1 red tube, 1 orange tube, 1 yellow tube and 1 green tube for storage (all to go to lab) + 1 red tube for ED near patient BNP.

Admitted patients

Please request a 12-hour troponin by admitting team on the bottom of the typed and written notes.

Discharged patients

If patient agreeable please book into the next Monday's 'troponin clinic' within 7 days of attendance. Held in the Clinical Research Facility, 2-4 pm, map and appointment form at reception. They will be given £30 expenses.

If patient not agreeable to return please still enrol in study.

ROSE study team

Dr Matthew Reed (CSO Academic Fellow, Dept of Emergency Medicine)
Long range pager 07659534490 Mobile 07913508126

Dr Alasdair Gray (Consultant, Dept of Emergency Medicine)
Prof David Newby (Prof of Cardiology, Cardiovascular Research Unit)
Dr Andrew Coull (Consultant, Department of Medicine for the Elderly)
Dr Keith Jacques (Specialist Registrar, Department of Emergency Medicine
Prof Robin Prescott (Professor of Statistics, University of Edinburgh)

ROSE main data collection form part B **Page 1**

Researcher checklist

1.	Patient's Name:	_____	
2.	DOB:	____ / ____ / _____	
3.	Sex	Male ☐	Female ☐
4.	Patient's phone number	_____	
5.	GP surgery:	_____	
6.	GP phone number:	_____	
7.	Patient eligible?	Yes ☐	No ☐
8.	Reason ineligible?	_____	
9.	Patient verbal consent?	☐	
	Patient written consent?	☐	
	Relative/welfare guardian written consent?	☐	
	Consent refused?	☐	
10.	Recruited? Prospectively ☐	Retrospectively ☐	
11.	ECG performed & attached	Yes ☐	No ☐
12.	BNP result obtained?	Yes ☐	No ☐
13.	BNP result checked on machine?	Yes ☐	No ☐
14.	Patient admitted?	Yes ☐	No ☐
15.	Admission troponin obtained?	Yes ☐	No ☐
16.	Patient discharged?	Yes ☐	No ☐
17.	Patient returned to Trop clinic?	Yes ☐	No ☐
18.	ECG reviewed by MR?	Yes ☐	No ☐
19.	ECG reviewed by cardiologist (DN)?	Yes ☐	No ☐
20.	Laboratory results chased?	Yes ☐	No ☐

ROSE main data collection form part B **Page 2**

21. Cardiac monitor abnormality detected during ED/CAA1 admission? Yes ☐ No ☐
22. Cause of syncope identified in ED? Yes ☐ No ☐
23. If so what? _____
24. Cause of syncope finally identified? Yes ☐ No ☐
25. If so what? _____
26. Hospital notes obtained? Yes ☐ No ☐
27. Complete records in trak system? Yes ☐ No ☐
28. GP contacted? Yes ☐ No ☐
29. Patient contacted? Yes ☐ No ☐
30. ISD contacted? Yes ☐ No ☐
31. Registrar General contacted? Yes ☐ No ☐
32. Follow-up possible available? Yes ☐ No ☐
33. If not, why not? _____
34. Is the patient alive at 1 month? Yes ☐ No ☐
35. If NO, Date of death: _____/_____/_____
36. Days after ED admission? _____
37. Cause of death: _____
38. How was cause ascertained? _____
39. Did patient have a 1/12 serious outcome? Yes ☐ No ☐
40. If so what? _____

_____

41. Data entry complete in database? Yes ☐ No ☐
42. Notes reviewed by expert panel? Yes ☐ No ☐
43. Obvious ED dx acc to expert panel? Yes ☐ No ☐

ECG interpretation (MR):

Rate ☐☐☐	QRS axis ☐☐☐	QTc int ☐☐☐
Sinus rhythm?	Yes ☐	No ☐
PR >200 msecs (1st degree heart block)?	Yes ☐	No ☐
Mobitz type II heart block?	Yes ☐	No ☐
Wenkebach heart block?	Yes ☐	No ☐
Bifascicular block?	Yes ☐	No ☐
Trifascicular block?	Yes ☐	No ☐
Complete heart block?	Yes ☐	No ☐
Sinus bradycardia <50?	Yes ☐	No ☐
Sinus pause >3 seconds?	Yes ☐	No ☐
ST elevation >1mm?	Yes ☐	No ☐
T wave inversion?	Yes ☐	No ☐
ST segment depression >1mm?	Yes ☐	No ☐
Pathological Q-waves	Yes ☐	No ☐
QTc > 450 msecs?	Yes ☐	No ☐
Left bundle branch block?	Yes ☐	No ☐
Right bundle branch block?	Yes ☐	No ☐
QRS duration >= 120 mseconds?	Yes ☐	No ☐
Number of ventricular ectopics?	☐☐	
Atrial tachycardia >100?	Yes ☐	No ☐
Narrow complex tachycardia >100?	Yes ☐	No ☐
Broad complex tachycardia >100?	Yes ☐	No ☐

Other abnormalities: _____

_____

_____

ECG interpretation (DN):

Rate ☐☐☐ QRS axis ☐☐☐ QTc int ☐☐☐

Sinus rhythm?	Yes ☐	No ☐
PR >200 msecs (1st degree heart block)?	Yes ☐	No ☐
Mobitz type II heart block?	Yes ☐	No ☐
Wenkebach heart block?	Yes ☐	No ☐
Bifascicular block?	Yes ☐	No ☐
Trifascicular block?	Yes ☐	No ☐
Complete heart block?	Yes ☐	No ☐
Sinus bradycardia <50?	Yes ☐	No ☐
Sinus pause >3 seconds?	Yes ☐	No ☐
ST elevation >1mm?	Yes ☐	No ☐
T wave inversion?	Yes ☐	No ☐
ST segment depression >1mm?	Yes ☐	No ☐
Pathological Q-waves	Yes ☐	No ☐
QTc > 450 msecs?	Yes ☐	No ☐
Left bundle branch block?	Yes ☐	No ☐
Right bundle branch block?	Yes ☐	No ☐
QRS duration >= 120 mseconds?	Yes ☐	No ☐
Number of ventricular ectopics?	☐☐	
Atrial tachycardia >100?	Yes ☐	No ☐
Narrow complex tachycardia >100?	Yes ☐	No ☐
Broad complex tachycardia >100?	Yes ☐	No ☐

Other abnormalities: _____

_____

_____

Laboratory results:

Haemoglobin		g/L
Haematocrit	.	ratio
WCC	.	$x10^9$/L
Neutrophil count	.	$x10^9$/L
Platelets		$x10^9$/L
Urea	.	mmol/L
Creatinine		umol/L
eGFR		ml/min
Na		mmol/L
K	.	mmol/L
TCO_2		mmol/L
Bilirubin		umol/L
ALT		U/L
ALP		U/L
GGT		U/L
Albumin		g/L
Ca^{2+}	.	mmol/L
PO^{4-}	.	mmol/L
Mg^{2+}	.	mmol/L
HS CRP		mg/L
Formal glucose	.	mmol/l
Troponin I	.	
Hours TnI after syncope		Hour

Appendix 2 Patient Consent Form

Please affix a patient identification label here

PATIENT CONSENT FORM

Title of Project: The ROSE study: A study to develop and validate a Clinical Decision Rule using history, examination, electrocardiographic (ECG) and biochemical markers, to predict one month outcome for patients presenting with syncope to the Emergency Department (ED). Study Number: 06/MRE00/107

Name of Researcher: Dr Matthew J Reed **Please initial box**

1. I confirm that I have read and understand the information sheet for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that sections of any of my medical notes may be looked at by responsible individuals from Lothian University Hospitals Trust or from regulatory authorities where it is relevant to my taking part in research and that data collected in the study may be linked to other records held by the NHS in Scotland. ☐
4. I agree that the blood tests taken as part of the study will be stored indefinitely for further analysis at a later date. My details will be removed from the sample and replaced with a study number. ☐
5. I agree to take part in the above study. ☐

Name of Patient	Date	Signature
Name of Person taking consent	Date	Signature

Patient written consent obtained? ☐ Verbal patient consent obtained? ☐

Appendix 3 Relative Consent Form

Please affix a patient identification label here

RELATIVE / GUARDIAN CONSENT FORM

Title of Project: The ROSE study: A study to develop and validate a Clinical Decision Rule using history, examination, electrocardiographic (ECG) and biochemical markers to predict one month outcome for patients presenting with syncope to the Emergency Department (ED). Study Number: 06/MRE00/107

Name of Researcher: Dr Matthew J Reed **Please initial box**

1. I confirm that I am either the patient's welfare guardian or that I am the patient's nearest relative and that there is no welfare guardian or nearer relative. ☐
2. I confirm that I have read and understand the information sheet for the above study and have had the opportunity to ask questions. ☐
3. I understand that my relative's participation is voluntary and that they are free to withdraw at any time, without giving any reason, without their medical care or legal rights being affected. ☐
4. I understand that sections of any of my relative's medical notes may be looked at by responsible individuals from Lothian University Hospitals Trust or from regulatory authorities where it is relevant to my relative's taking part in research and that data collected in the study may be linked to other records held by the NHS in Scotland. ☐
5. I agree that the blood tests taken from my relative as part of the study will be stored indefinitely for further analysis at a later date. My relative's details will be removed from the sample and replaced with a study number. ☐
6. I agree for my relative to take part in the above study. ☐

Name of Patient _____ Name of Relative or Welfare Guardian (delete as appropriate) _____

Relationship to Patient _____ Date _____ Signature _____

Name of Doctor taking consent _____ Date _____ Signature _____

Appendix 4 GP Information Sheet

Emergency Department,
Royal Infirmary of Edinburgh,
51 Little France Crescent,
Edinburgh,
EH16 4SA.

0131 242 1300

Dear Dr

Re: Patient's Name:
Patient's Date of Birth:
Patient's Address:

The ROSE study: A study to develop and validate a Clinical Decision Rule using history, examination, electrocardiographic (ECG) and biochemical markers, to predict one month outcome for patients presenting with syncope to the Emergency Department (ED).

Study Number: 06/MRE00/107

This is a letter to inform you that one of your patients recently attended our Emergency Department having suffered an episode of syncope, and has consented to take part in the prospective study that is detailed above.

Participation in the study involves a standard history, examination, ECG and blood investigations in the ED, routine practice for all patients presenting with syncope. Patients will also undergo a point of care brain natriuretic peptide (BNP) test. We hypothesize that this protein may be of use in predicting outcome in patients who present with syncope. The patient has also given consent to allow us to look at sections of their medical records and link these to other NHS records.

We may need to contact you in 3 months time in writing, in order to obtain further information as to the progress of your patient. We would be very grateful if you could spare a few moments of your time to help if this is required.

This study has received ethical approval from the Multi Centre Research Ethics Committee for Scotland, Committee A and management approval from Lothian NHS. The Independent Adviser for the study is Professor Robertson. Any queries or requests for further information regarding this study including access to the results of the study should be directed to me at the above address.

Kind regards,

Dr Matthew Reed,

Consultant in Emergency Medicine and Chief Scientist Office Clinical Research Training Fellow.

Appendix 5 GP follow-up letter

Emergency Department,
Royal Infirmary of Edinburgh,
51 Little France Crescent,
Edinburgh,
EH16 4SA.

Phone: 0131 242 1334
Fax: 0131 242 1339

Dear Dr

Patient's Name:

Patient's Date of Birth:

Patient's Address:

The ROSE study: A study to develop and validate a Clinical Decision Rule using history, examination, electrocardiographic (ECG) and biochemical markers, to predict one month outcome for patients presenting with syncope to the Emergency Department (ED).

Study Number: 06/MRE00/107

Further to our recent letter to inform you that the above patient has been enrolled into the ROSE study, I would be grateful if you could complete the form over the page and fax it back to us to 0131 242 1339 for the attention of Dr Matt Reed.

Kind regards,

Dr Matthew Reed,

Consultant in Emergency Medicine and Chief Scientist Office Clinical Research Training Fellow.

Patient's Name:

Patient's Study number:

Is the patient alive?	Yes	No
If not, date of death?	_____	
<u>Since their attendance in A&E have they had:</u>		
A myocardial infarction?	Yes	No
A 24 hour tape showing VT/VF or asystole?	Yes	No
A pacemaker or internal cardiac defibrillator inserted?	Yes	No
If so on what date?	_____	
A pulmonary embolus	Yes	No
A CVA or subarachnoid haemorrhage	Yes	No
A hospital admission not to the RIE?	Yes	No
If so where?	_____	
Did this include a haemorrhage requiring a blood transfusion of two units or more?	Yes	No
or an acute surgical procedure or endoscopic procedure?	Yes	No
If so what procedure?	_____	

Many thanks

Appendix 6 Patient Information Sheet

Emergency Department,
Royal Infirmary of Edinburgh,
51 Little France Crescent,
Edinburgh,
EH16 4SA.

Telephone No: 0131 242 1300

Study Title:

The ROSE study: A study to develop and validate a Clinical Decision Rule using history, examination, electrocardiographic (ECG) and biochemical markers, to predict one month outcome for patients presenting with syncope to the Emergency Department (ED).
(Study Number: 06/MRE00/107)

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. You should not take part if you feel that you have not been given sufficient time to make your decision.

What is the purpose of the study?
This study aims to improve the care of some patients who come to the Emergency Department (ED). We are investigating people who attend the department having had a collapse (medically termed syncope). There are many medical causes for a person to collapse and we are aiming to improve our ability to decide which patients require to be admitted to hospital, which patients need further investigations in the outpatients department, and which patients do not require any further tests.

Why have I been chosen?
You have been chosen to take part in the study because you attended the ED today with a collapse.

Do I have to take part?
It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and will be asked to sign two copies of a consent form, one of which you will keep. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?
If you decide to participate in the study, the ED doctor will find out what has happened to you and examine you in the normal way. Some of this information will be recorded for the purposes of the study. You may have a routine ECG and routine blood tests performed. You will also have four separate research blood samples taken which will total no more than 13mls (3 teaspoons) of blood. A drop of blood from one of the research blood samples will be used to measure the level of a protein called Brain Natriuretic Peptide that is found in the blood, and which may be useful in diagnosing patients who have collapsed.

A few patients may be asked to return to the ED during the following week for a repeat blood test. If you are asked to do this we will fully reimburse you any travel expenses.

Some patients will also have a longer 5 minute ECG recording taken during their stay in the ED. This tracing will be subjected to further computer analysis.

All research blood tests taken as part of the study will be stored indefinitely. Further analysis may be undertaken on these samples at a later date as part of the ROSE study. Your details will be removed from the sample and replaced with a study number.

We may also be looking at some of your medical notes relevant to this visit and some information that is collected by the study investigators may also be linked to other records held by the NHS in Scotland. We will notify your GP that you

have participated in this study and may also contact your GP over the next 3 months for further information. We will not ask about any other information that is not related to the collapse you have had today.

What are the possible disadvantages and risks of taking part?
There are no adverse effects associated with this study and the confidentiality of all data collected will be ensured. The study is a non-therapeutic one.

What are the possible benefits of taking part?
There are no direct benefits to your care today, however through this study we hope to improve the care given to patients who may be seen in the future.

Will my taking part in this study be kept confidential?
All information that is collected about you during the course of the research will be kept strictly confidential. Any information about you that leaves the hospital will have your name and address removed so that you cannot be recognised from it.

What will happen to the results of the research study?
We are hoping to study 1,000 patients in total and the study is anticipated to last for 2 years. We hope that the results will be published during the following year. You will not be identified in any publication or study report.

Who has reviewed the study?
This study has received ethical approval from the Multi Centre Research Ethics Committee for Scotland, Committee A and management approval from Lothian NHS. The independent adviser for the study is Professor Robertson.

Contact for Further Information.
Any later queries or requests for further information regarding this study including access to the results of the study, should be directed me at the above address.

Thank you for reading this.

Dr Matthew Reed

CSO Research Fellow in Emergency Medicine.

Appendix 7 Patient Information Sheet for Relatives

Emergency Department,
Royal Infirmary of Edinburgh,
51 Little France Crescent,
Edinburgh,
EH16 4SA.

Telephone No: 0131 242 1300

Study Title:

The ROSE study: A study to develop and validate a Clinical Decision Rule using history, examination, electrocardiographic (ECG) and biochemical markers, to predict one month outcome for patients presenting with syncope to the Emergency Department (ED).
(Study Number: 06/MRE00/107)

Your relative has been invited to take part in a research study. Before you decide whether they should participate it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. You should not consent for your relative to take part if you feel that you have not been given sufficient time to make your decision.

What is the purpose of the study?
This study aims to improve the care of some patients who come to the Emergency Department (ED). We are investigating people who attend the department having had a collapse (medically termed syncope). There are many medical causes for a person to collapse and we are aiming to improve our ability to decide which patients require to be admitted to hospital, which patients need further investigations in the outpatients department, and which patients do not require any further tests.

Why has my relative been chosen?
Your relative has been chosen to take part in the study because they have attended the ED today with a collapse.

Do they have to take part?
It is up to you to decide whether or not they should take part. If you do decide they should take part you will be given this information sheet to keep and will be asked to sign two copies of a consent form, one of which you will keep. If you decide that they will take part you are still free to withdraw your relative at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care your relative receives.

What will happen to my relative if they take part?
If you decide your relative will participate in the study, the ED doctor will find out what has happened to them and examine them in the normal way. Some of this information will be recorded for the purposes of the study. They will have a routine ECG and routine blood tests performed. They will also have four separate research blood samples taken which will total no more than 13mls (3 teaspoons) of blood. A drop of blood from one of the research blood samples will be used to measure the level of a protein called Brain Natriuretic Peptide that is found in the blood, and which may be useful in diagnosing patients who have collapsed.

A few patients may be asked to return to the ED during the following week for a repeat blood test. If your relative is asked to do this we will fully reimburse them any travel expenses.

All research blood samples taken as part of the study will be stored indefinitely. Further analysis may be undertaken on these samples at a later date as part of the ROSE study. Your relative's details will be removed from the sample and replaced with a study number.

Some patients will also have a longer 5 minute ECG recording taken during their stay in the ED. This tracing will be subjected to further computer analysis.

We may also be looking at some of your relative's medical notes relevant to this visit and some information that is collected by the study investigators may also be linked to other records held by the NHS in Scotland. We will notify

your relative's GP that they have participated in this study and may also contact their GP over the next 3 months for further information. We will not ask about any other information that is not related to the collapse they have had today.

What are the possible disadvantages and risks of taking part?
There are no adverse effects associated with this study and the confidentiality of all data collected will be ensured. The study is a non-therapeutic one.

What are the possible benefits of taking part?
There are no direct benefits to your relative today, however through this study we hope to improve the care given to patients who may be seen in the future.

Will the fact that my relative has taken part in this study be kept confidential?
All information that is collected about your relative during the course of the research will be kept strictly confidential. Any information about your relative that leaves the hospital will have their name and address removed so that they cannot be recognised from it.

What will happen to the results of the research study?
We are hoping to study 1,000 patients in total and the study is anticipated to last for 2 years. We hope that the results will be published the following year. Your relative will not be identified in any publication or study report.

Who has reviewed the study?
This study has received ethical approval from the Multi Centre Research Ethics Committee for Scotland, Committee A and management approval from Lothian NHS. The independent adviser for the study is Professor Robertson.

Contact for Further Information.
Any later queries or requests for further information regarding this study including access to the results of the study, should be directed me at the above address.

Thank you for reading this.

Dr Matthew Reed
CSO Research Fellow in Emergency Medicine

Appendix 8 UK ED syncope survey

Dear Colleague, 05/11/2007

We are in the process of conducting a large derivation and validation study to derive a clinical decision rule using history, examination, ECG characteristics and novel biochemical markers to predict adverse outcome in patients presenting to UK emergency departments with syncope. The study is called the ROSE (Risk stratification Of Syncope in the Emergency department) study and we hope to report our results at the end of next year.

As part of this study we would like to look at the current management of syncope patients who present to UK Emergency Departments, and what scope is available for improving practice.

We would be extremely grateful if you could spare a few moments of your time to complete the attached questionnaire and return it in the stamped addressed envelope to:

Dr Matthew Reed,
Emergency Department,
Royal Infirmary of Edinburgh,
51 Little France Crescent,
Edinburgh,
EH16 4SA.

We will write again in 4 weeks if we have not heard from you and follow this up with a telephone call to ensure we are able to obtain as best response as possible. Many thanks for your time in completing this survey.

Dr Matthew Reed

Consultant in Emergency Medicine
& CSO Academic Fellow, Edinburgh.

Milla Stockley

SSc student,
Edinburgh University.

On behalf of the ROSE study investigators:

Dr Alasdair Gray	(Consultant, Dept of Emergency Medicine)
Prof David Newby	(Prof of Cardiology, Cardiovascular Research Unit)
Dr Andrew Coull	(Consultant, Department of Medicine for the Elderly)
Dr Keith Jacques	(Specialist Registrar, Dept. of Emergency Medicine)
Prof Robin Prescott	(Professor of Statistics, University of Edinburgh)

This survey has been approved by BAEM

UK Emergency Department Syncope Survey

Q1 Do you have syncope guidelines for use in your ED?

Yes (go to Q2) ☐ No (go to Q5) ☐

If 'yes' please enclose a copy of these along with the completed questionnaire

Q2 Are these based on any of the following?

- **European Society of Cardiology guidelines** ☐
- **American College of Emergency Physicians guidelines** ☐
- **American College of Physicians guidelines** ☐
- **OESIL syncope score** ☐
- **San Francisco Syncope Rule** ☐
- **Other, if so what?** _____

Q3 In what format are these guidelines?

Paper form ☐ **Electronic form** ☐

Poster display ☐ **(Tick any which apply)**

Q4 Are these guidelines **ED use only guidelines?** ☐ **General hospital guidelines?** ☐

Q5 Does your hospital have **Separate front doors for Medical/GP referral/ED patients?** ☐

A single front door for Medical/GP referral/ED patients? ☐

Q6 Does your ED have an observation ward/clinical decision unit?

Yes (go to Q7) ☐ No (go to Q8) ☐

Q7 Do you admit syncope patients in your ED observation ward/clinical decision unit?

Yes ☐ No ☐

Q8 Does your hospital have a specialist syncope outpatient clinic?

Yes (go to Q9) ☐ No (go to Q11) ☐

Q9

Is this run by a Cardiologist? ☐ **Neurologist** ☐

General Physician ☐ **Emergency Physician** ☐

GP specialist ☐ **Nurse specialist** ☐

Geriatrician ☐ **Other** _____ ☐

Q10 Is this accessible by referral from the ED?

Yes ☐ No ☐

Q11 Do you think more research based guidelines would be useful when managing patients presenting with syncope to the ED?

Yes ☐ No ☐

Q12 Do you have access to near patient testing in your ED?

Yes (go to Q13) ☐ No (go to Q14) ☐

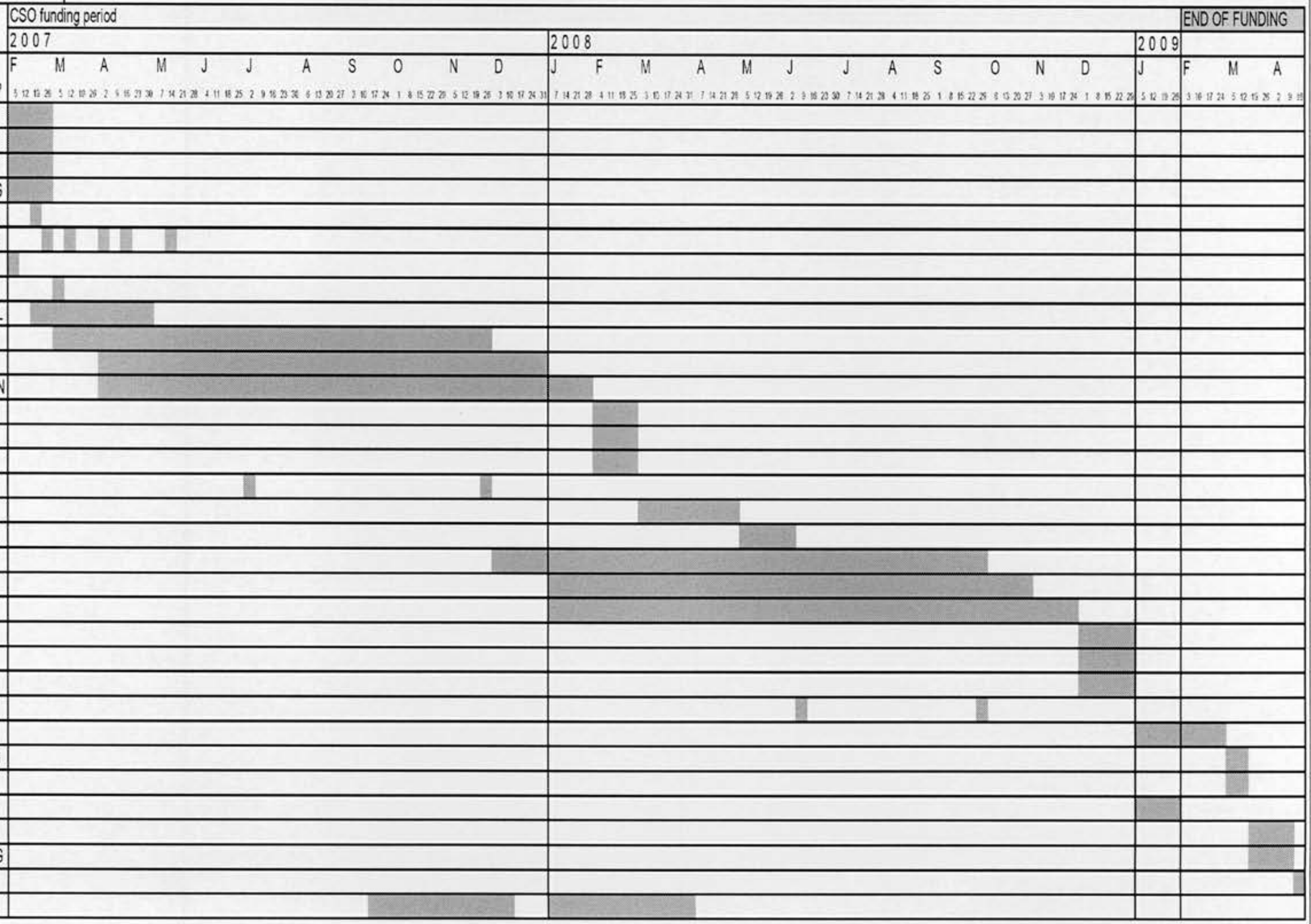
Q13 Do you use near patient BNP testing in your ED?

Yes ☐ No ☐

Q14 Name of ED/Hospital:

Appendix 9 Study Gantt chart

Gantt chart for ROSE study	Modified: 13 02 2007	
TASK	DURATION	WHO?
Designing of Study Data Collection Form	1m	MR
Designing of Study paperwork	1m	MR
Submission of ethics revision	1m	MR
Study protocol	1m	MR CRG
Core research group meetings	1d	CRG
MR Supervisor meetings	1d	MR AG
Ordering of Biosite products	1m	MR
Submission of protocol to journal	1w	MR
Database designing	3m	MR RL
Prospective derivation study (500 patients)	9m	MR
Patients 1 month post ED derivation visit	9m	MR
Patient derivation study follow up	10m	MR ? RN
Expert committee to review serious outcomes	1m	CRG
Expert committee to review enrolment criteria	1m	CRG
Construction of derivation patient flow diagram	1m	CRG
Cardiology review of derivation ECG data	2w	DN
Analysis of derivation study data	2m	PP RL
Derivation of Clinical Decision Rule	1m	PP RL
Prospective validation study (500 patients)	9 m	MR
Patients 1 month post ED validation visit	9 m	MR
Patient validation study follow up	10m	MR
Expert committee to review serious outcomes	1m	CRG
Expert committee to review enrolment criteria	1m	CRG
Construction of derivation patient flow diagram	1m	CRG
Cardiology review of validation ECG data	2w	DN
Analysis of validation study data	2m	PP RL
Final analysis	2w	PP CRG
Development of guidelines	2w	CRG
Repeat literature review	1m	MR
Reporting and dissemination	1m	CRG
Scientific write up	1m	MR CRG
Submission to journal	1m	MR
MR Modules in Public Health Medicine		



Appendix 10 Published papers

REVIEW

Collapse query cause: the management of adult syncope in the emergency department

M J Reed, A Gray

Emerg Med J 2006;**23**:589–594. doi: 10.1136/emj.2005.032136

Syncope is a commonly encountered problem in the emergency department (ED). Its causes are many and varied, some of which are potentially life threatening. A review was carried out of relevant papers in the available literature, and this article attempts to assimilate current evidence relating to ED management. While the cause of syncope can be identified in many patients, and life threatening conditions subsequently treated, a risk stratification approach should be taken for those in whom a cause is not identified in the ED. Aspects of the history and examination that may help identify high risk patients are explored and the role of investigations to aid this stratification is discussed. Identifying a cardiac cause for syncope is a poor prognostic indicator. Patients with unexplained syncope who have significant cardiac disease should therefore be investigated thoroughly to determine the nature of the underlying heart disease and the cause of syncope, although presently there is little evidence that this improves their dismal prognosis. This risk stratification approach has led to the development of several clinical decision rules, which are discussed along with current international guidelines on syncope management. This review suggests that presently the American College of Emergency Physicians guidelines are the most useful aids specific to the management of syncope in the ED; however, the Osservatorio Epidemiologico sulla Sincope nel Lazio (OESIL) score may also be a useful ED risk stratification tool

Syncope is a transient loss of consciousness with an inability to maintain postural tone followed by a spontaneous recovery.[1] The word derives from a Greek term meaning "to cut short" and may have been first described by Hippocrates.[2] Syncope accounts for approximately 3% of emergency department (ED) visits and between 1 and 6% of acute hospital medical admissions, affecting 6 per 1000 people per year.[2 3] Clinical assessment of syncope is challenging, owing to the heterogeneous nature of underlying causes, ranging from benign neurocardiogenic syncope to potentially fatal dysrhythmias and pulmonary embolism.

There is some evidence of suboptimal clinical management of patients with syncope. Thakore *et al* in 1999 looked at practice in one UK ED and showed that few patients had relevant syncope symptoms documented and 25% of patients did not have an electrocardiogram (ECG) recorded. In addition, 28% of patients with an abnormal ECG and 40% with a history of organic heart disease were sent home from the ED.[4]

The aim of this article was to review and assimilate all available evidence for the management of adult patients presenting to the ED with syncope.

METHODS

Search strategy

To address the aim, a search strategy was devised, using the search terms [syncope, vasovagal/ or syncope/ or syncope.mp AND emergency service, hospital/ or emergency department.mp. or emergency medical services/,] *b*. The search was applied via the OVID interface, to MedLine (1966 to October 2005 week 2), EMBASE (1980 to 2005 week 42) and the Cochrane Database of Systematic Reviews. All articles relevant to the management of adult patients with syncope in the ED were included. Any articles that did not focus on the management of adult syncope within the ED were rejected.

In total, 292 articles were identified from the search strategy, of which 82 were thought to be relevant. To prevent selection bias, no limits were placed on the search. The abstracts of all papers identified were read to determine relevance. The full texts of relevant articles were then obtained and read to determine if they should be included in the review. The references of all papers designated for review inclusion were also hand searched to identify further suitable studies.

RESULTS AND DISCUSSION

History

In treating syncope, a history of transient loss of consciousness followed by spontaneous recovery must be elicited. A thorough history and physical examination is able to determine the reason for syncope in approximately 40% of patients.[5–8] Most patients do not remember their syncopal episode. Some patients can recall the event as it may terminate just prior to the loss of consciousness ("presyncope"). It is important to identify

See end of article for authors' affiliations

Correspondence to: Dr M J Reed, Emergency Department, Royal Infirmary of Edinburgh, 51 Little France Crescent, Edinburgh EH16 4SA, UK; mattreed1@hotmail.com

Accepted for publication 13 March 2006

Abbreviations: ACEP, American College of Emergency Physicians; ACP, American College of Physicians; artery disease, CCF, congestive cardiac failure; ECG, electrocardiogram; ED, emergency department; MI, myocardial infarction; OESIL, Osservatorio Epidemiologico sulla Sincope nel Lazio; PVC, premature ventricular contraction

features in the history that may point to seizure activity, the most important of which is the presence of a post-ictal phase. While confusion may be present immediately after syncope, this should not last for more that a minute.[1] Other discriminators such as tonic-clonic activity, incontinence, and tongue biting may help, but do not in isolation rule out syncope if a period of cerebral anoxia has occurred.[9] Seizure activity that is thought not to be primarily due to a period of cerebral anoxia (that is, epilepsy) should not be classified as syncope.

The presence of presyncopal symptoms such as nausea, diaphoresis, dizziness, and a feeling of warmth may suggest vaso-vagal syncope.[7 10 11] Precipitant factors (micturition and coughing) may suggest situational syncope, and a positional aspect (syncope precipitated by rising from a sitting position) may suggest orthostatic syncope. Kapoor *et al* found that vaso-vagal syncope, orthostatic hypotension, and situational syncope were the diagnoses most commonly made on the basis of history and examination alone, and accounted for 30% of syncope presentations.[6]

Other important symptoms prior to the syncopal event include chest pain, sudden onset of headache or dyspnoea, palpitations, back pain, or focal neurological deficits. The presence of any of these may suggest an alternative serious cause. A brief or absent presyncopal period may be associated with syncope of a cardiac nature, especially a dysrhythmia.[11] Here, an average length of presyncopal symptoms of 3 seconds has been reported.[10] Syncope associated with neurocardiogenic (vaso-vagal) syncope has been reported to last an average of 2.5 minutes.[1 10] Recurrent episodes of syncope, while leading to an increased likelihood of injury, are not associated with major morbidity. Mortality decreases with increasing syncope frequency.[6 12] Calkins *et al* found that patients experiencing syncope secondary to dysrhythmias were more likely to be male, aged >54 years, to have less than 5 seconds of presyncope warning, and less likely to have had previous syncope episodes, compared to those patients with neurocardiogenic syncope. This latter group were more likely to have palpitations, blurred vision, and feelings of nausea, warmth and light headedness prior to the syncope episode, and feelings of nausea, warmth, dizziness, and fatigue afterwards.[11]

A witness history should be sought and a drug history taken to identify the use of antihypertensive or other cardiac medication, and drugs that cause bradycardia, hypotension, or prolong the QT interval (erythromycin, quinine and major tranquilisers). Nitrate use immediately prior to the syncopal episode is associated with glyceryl trinitrate syncope. A menstrual history should also be taken in women of childbearing age, as syncope is a not uncommon presentation of ectopic pregnancy. In addition, neurocardiogenic syncope is relatively common in early pregnancy.

Some patients presenting with syncope may be under the influence of alcohol or recreational drugs, making a thorough history difficult. While these substances may lead to collapse, syncope is unlikely to occur as a direct consequence of either alcohol or recreational drugs. These patients should be assessed at the time of presentation with a thorough examination and ECG; however, subsequent assessment of risk and additional investigations may need to wait until the patient is more compliant.

Finally, a family history of cardiac disease or sudden unexplained family death or history of syncope precipitated by exercise raise the possibility of hypertrophic cardiomyopathy, Brugada's syndrome, or pre-excitation disorders such as congenital long QT syndrome, and arrhythmogenic right ventricular dysplasia, which can be precipitated by a sympathetic surge.

Examination

A detailed physical examination should be performed, vital signs obtained, and a point of care blood glucose measurement taken. The cardiovascular system should be specifically examined, looking for a postural drop (a fall of ≥20 mmHg, or a fall to <90 mmHg after standing for at least 3 minutes), a displaced apex, valve lesions, the presence of cardiac failure, carotid bruits, and a ventricular pause of >3 seconds precipitated by carotid sinus massage.[1] This final test is diagnostic for carotid sinus hypersensitivity, and should be performed if syncope may have been precipitated by neck movements or pressure on the neck. It is important to first exclude the presence of a carotid bruit and to be aware of the risk of precipitating a prolonged sinus pause or an episode of hypotension. Patients should also have intravenous access and be in an area where resuscitation equipment is available if required. Neurological examination should attempt to identify signs suggestive of seizure activity pointing towards a primary neurological seizure rather than true syncope. Finally, evidence of related trauma should be sought and a rectal examination performed to identify gastrointestinal haemorrhage if suggested by the history.

Oh *et al*[7] prospectively studied 497 patients with syncope to determine whether symptoms and comorbidities predicted adverse outcome. History and physical examination identified a cause in 222 patients (47%). In the remaining patients, the absence of presyncopal nausea and vomiting (odds ratio (OR) = 7.1) and the presence of ECG abnormalities (OR = 23.5) were predictors of dysrhythmic syncope.

Investigations

Despite full blood count and urea and electrolyte estimation seeming reasonable investigations in syncope, laboratory investigations have not been shown to discriminate in the management of syncope,[10 14 15] except for a profoundly low haematocrit,[13] and current guidelines do not recommend routine testing.[16 17] In one study of syncopal patients, two of 134 patients were found to be hypoglycaemic,[10] and one, later diagnosed with diuretic induced orthostatic hypotension, was hyponatremic.[8] Of 134 patients with syncope secondary to gastrointestinal haemorrhage, four had an abnormal haematocrit that dropped with rehydration;[1] however, on each occasion the diagnosis was suspected on clinical grounds. A urinary β-HCG test should be considered in all women of childbearing age to rule out an ectopic pregnancy.

The only studies that have shown brain computed tomography and electroencephalogram to be helpful have included primary neurological seizures as a cause of syncope. All other studies have shown no benefit in performing these or any radiological investigations in the management of syncope.[6 10 18–20]

Electrocardiogram

A standard 12 lead ECG is warranted in all cases of syncope unless the history and physical examination reveal an obvious non-cardiac cause. This initial ECG is normal in most patients with syncope.[5 6 10 19–21] Martin *et al* suggested that the ECG is diagnostic in only 2% of patients,[10] while Kapoor *et al* found that 28 of 433 patients (6%) had a diagnostic initial ECG.[6] Martin *et al* also found that the presence of an abnormal ECG (defined as any abnormality of rhythm or conduction, ventricular hypertrophy, or evidence of prior myocardial infarction, but excluding non-specific ST segment and T wave changes) was a multivariate predictor for dysrhythmia or death within one year of syncope.[8] A further study showed that an abnormal ECG, defined as rhythm or conduction abnormality, atrioventricular block, signs of an old myocardial infarction (MI), left or right ventricular hypertrophy or frequent premature ventricular

contractions (PVCs), was a predictor for dysrhythmic syncope.[7] Equally, a normal ECG is associated with negative electrophysiology studies,[6] and a low risk for syncope secondary to a cardiovascular cause.[8 16 22 23] The ECG also allows assessment of the QT interval and may suggest disorders such as Wolff-Parkinson-White syndrome.[24]

The current European Society of Cardiology syncope guidelines[16] document the ECG abnormalities that increase the risk of a syncope secondary to dysrhythmia: bifascicular block, QRS >0.12 seconds, Mobitz second degree atrioventricular block, sinus bradycardia (<50 bpm), sinoatrial block, sinus pause >3 seconds, pre-excited QRS complexes, prolonged QT interval, signs of Brugada syndrome (right bundle branch block, ST segment elevation in leads V1–V3) or arrhythmogenic right ventricular dysplasia (epsilon wave or localised QRS >110 ms in V1–V3, or inverted T waves in V2 and V3 without right bundle branch block), and Q waves suggesting MI. It is suggested that patients with these abnormalities should be admitted for monitoring and be investigated for dysrhythmic syncope. There is no evidence that any of these findings are associated with an early adverse outcome and no studies have been powered to assess the prognostic value of ECG abnormalities.

Other cardiac investigations

For patients considered at risk of having an arrhythmic cause for their syncope, longer electrocardiogram assessment in the form of 24 hour tape monitoring and loop recording may be considered on either an inpatient or outpatient basis. These investigations have good sensitivity; however, patients experiencing arrhythmias may not demonstrate abnormalities during the monitoring period. While arrhythmias demonstrated during routine ED monitoring are obviously diagnostic, more prolonged monitoring does not form part of ED investigation.

Echocardiography is also considered part of syncope investigation. There is no evidence yet that ED echocardiography is able to aid ED risk stratification; however, early echocardiography may prove helpful in the future.

Cardiac markers

The routine measurement of cardiac markers in adult patients presenting to the ED with syncope has a diagnostic yield for acute MI of <1%.[25–27] This may be higher in elderly patients who are more likely to present with atypical symptoms of MI such as syncope.[28] Even in this group, the number of patients who do not have other features suggestive of MI is small.[25] Other groups prone to "silent" MI such as those with diabetes have not been investigated. There is no evidence that raised cardiac markers have any prognostic value.[27 29]

Diagnosis of syncope

In the 1980s, the commonest underlying diagnosis of syncope was vaso-vagal syncope (37–40%).[5 6 10 14 18 19 30] Other diagnoses included dysrhythmia (8–20%), orthostatic hypotension (8–10%), situational syncope (3–8%), organic heart disease (4–8%) and carotid sinus syncope (1%). In 31–47% of patients, no cause of syncope was found.[5 6 10 14 18 19 30] The underlying reason for syncope is now more likely to be elicited with increased availabilities of tilt testing, and 24 hour tape monitoring and loop recording; however, commonly it is not clear after initial ED assessment.[31] The most recent study employing diagnostic algorithms and newer diagnostic modalities suggests that unexplained syncope still accounts for 14% of all patients (table 1).[31]

Stratification by cause of syncope

In 1983, Kapoor *et al*[19] published the first prospective study of 204 syncopal patients. A cardiovascular cause (dysrhythmia, aortic stenosis, MI, pulmonary embolus, dissecting aortic aneurysm) was determined in 53 patients, a non-cardiovascular cause in 54, and in 97 patients no cause was identified. At 12 months, mortality was 14%. Mortality was greater in the patients in whom a cardiovascular cause had been identified (30%) than in the patients in whom a non-cardiovascular cause had been identified (12%), or in those in whom no cause had been found (6.4%). Sudden death (defined as death within 24 hours of the onset of symptoms) was found to be greater in the patients in whom a cardiovascular cause had been identified (24%) compared with a non-cardiovascular cause (4%) and an unknown cause (3%). This study was the first to highlight the greater risk to a patient whose syncope is due to a cardiac cause.

Soteriades *et al*[32] studied 7814 participants of the Framlingham heart study. Of these, 822 had syncope in the 17 years of follow up (6.2 per 1000 person years). Vaso-vagal

Table 1 Diagnosis of cause of syncope in 650 patients.

Cause of syncope	n	%
Non-cardiac causes	456	70
Vasodepressor syncope	242	37
Orthostatic hypotension	158	24
Neurological	30	5
Psychiatric	11	2
Other	9	1.5
Carotid sinus hypersensitivity	6	1
Unknown	92	14
Cardiac	69	11
Arrhythmias	44	7
Sinus bradycardia or pause	15	2
Atrioventricular block	15	2
Ventricular tachycardia	9	1.5
Supraventricular tachycardia	4	0.5
Pacemaker malfunction	1	0.2
Acute coronary syndrome	9	1.5
Aortic stenosis	8	1
Pulmonary embolism	8	1
Incompletely assessed	33	5

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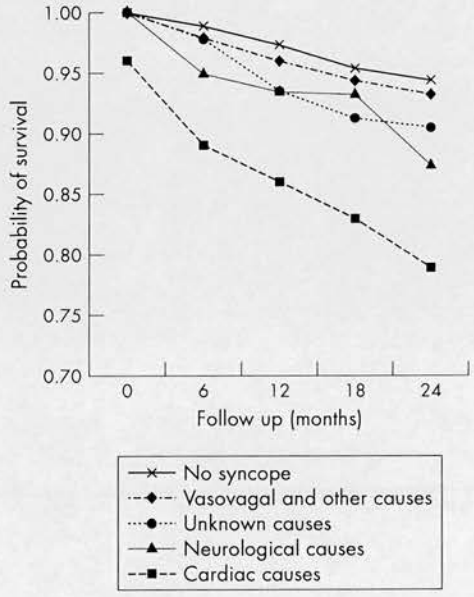

Figure 1 Overall survival of participants with syncope according to cause, and participants without syncope, among 7814 participants of the Framlingham heart study. Adapted from Soteriades *et al*,[3] with permission from the publishing division of the Massachusetts Medical Society.

syncope, the most common cause (21.2%), was not associated with any increased risk of death; however, a cardiac cause for syncope, found in 9.5%, was associated with a two fold increase in death, and a 6 month mortality rate exceeding 10% (fig 1). Getchell *et al* studied elderly hospitalised patients (mean age 73 years) presenting with syncope, and showed that mortality was not associated with a cardiac cause for syncope, but rather with age and comorbid illnesses.[33]

Subsequent studies controlling for cardiac mortality have showed that the higher mortality in patients with syncope due to a cardiovascular cause is largely related to underlying cardiovascular disease.[7 21 34] A study comparing patients with and without syncope, who were matched for cardiac disease, showed that syncope itself was not a significant predictor of 1 year survival,[21] however male sex, age >55 years and congestive heart failure were significant predictors. Middlekauff *et al* in 1993 studied 491 patients with advanced cardiac failure, 60 of whom had an episode of syncope. The 1 year mortality was greater in the patients with cardiac failure who had a history of syncope, compared to a matched group of patients with cardiac failure and without a syncope history (45% versus 12%). The major predictor of sudden death, however, was poor left ventricular function, not whether the cause of the syncope was cardiac or not.[34] This study demonstrated syncope itself to be a good predictor of mortality. Whether these results are applicable to other patient populations is unclear.

It therefore seems it is the presence of significant underlying heart disease that is associated with a poor prognosis in syncope. It is likely that the presence of cardiac failure, commonly secondary to coronary artery disease, predisposes the patient to dysrhythmias and consequent syncope or sudden death. Patients with syncope and with signs of cardiac failure should be notionally high risk patients and therefore should be investigated to delineate underlying heart disease and the cause of syncope, in an attempt to reduce mortality.[21 35]

Clinical decision rules

Martin *et al* prospectively developed and validated a risk stratification system for patients presenting to the ED with syncope.[8] In total, 252 patients were enrolled into a derivation cohort and 374 into a validation group. Four factors were predictive of 1 year mortality or dysrhythmia occurrence. These were abnormal presenting ECG findings (rhythm abnormalities, frequent PVCs, conduction disorders, left or right ventricular hypertrophy, short PR interval, evidence of an old MI, and atrioventricular block), a history of ventricular dysrhythmias, a history of congestive cardiac failure, and age >45 years. The 1 year mortality and dysrhythmia risk in patients with none of the four risk factors was 4.4–7.3%, increasing to 57.6–80.4% in patients with three risk factors.

Emphasis subsequently moved from the importance of making an underlying diagnosis in syncopal patients to risk stratification of patients into groups correlating with mortality. As the underlying conditions associated with short term mortality in syncope are related to structural cardiac disease and dysrhythmias, the rationale behind risk stratification is to focus resources into monitoring and investigating these high risk patients to reduce mortality.

Oh *et al*[7] found that history and physical examination was able to determine a cause in 47% of patients. The only independent predictor of 1 year mortality was the presence of underlying cardiac disease (defined as coronary artery disease, valvular disease, cardiomyopathy, congestive cardiac failure, or other organic heart disease found clinically or during investigations). Crane[36] conducted the only UK ED study of syncope outcome. This retrospective study of 210 patients presenting during an 8 week period showed that it was possible to stratify UK ED patients with syncope according to the American College of Physicians (ACP) guidelines.[37 38] Patients in the ACP group 1 (high risk), had a 1 year mortality rate of 36%, compared to patients assigned to ACP group 2 (intermediate risk) (14%), and ACP group 3 (low risk) (0%).

Shen *et al*[39] showed that patients in an intermediate risk group can be investigated in a ED based syncope unit, leading to an increased diagnostic yield, reduced hospital admission, and length of hospital stay, without increasing mortality.

Colivicchi *et al*[40] performed a six centre study that recruited 270 patients into a derivation study and 328 into a validation group. They developed a risk score (Osservatorio Epidemiologico sulla Sincope nel Lazio (OESIL) score) based on four characteristics: age >65 years, a clinical history of cardiovascular disease, syncope without prodromal symptoms, and an abnormal ECG. The presence of each characteristic scored 1 point. The authors found that 1 year mortality increased with increasing risk score and suggested that the tool could therefore be used in the assessment of ED patients with syncope (fig 2).

Sarasin *et al*[41] prospectively recruited 175 Swiss patients with unexplained syncope after ED investigation into a derivation study, and 269 similar US patients into a validation group. They found that predictors for dysrhythmic syncope were abnormal ECG, a history of congestive cardiac failure, and age >65 years. Risk of dysrhythmia (diagnosed by defined 24 hour Holter or loop recorder abnormalities) rose from 0–2% in patients with no risk factors to 6–17% in patients with one risk factor, 35–41% in those with two, and 27–60% in those with all three risk factors. They concluded that a risk score based on clinical and ECG factors is able to identify patients in the ED at risk of dysrhythmia.

The most recent and largest derivation study on syncope risk stratification focused on short term risk (probably more relevant to ED practice) and was performed by Quinn *et al*.[13] They prospectively studied 684 patients who presented to a US ED with syncope, 79 of whom experienced a serious 7 day outcome. Of the 50 studied predictor variables, 26 were associated with a serious outcome. A clinical decision rule (the San Francisco syncope rule) was devised using five risk factors: abnormal ECG, anaemia (haematocrit <30%), complaint of shortness of breath, systolic hypotension (<90 mmHg), and a history of congestive cardiac failure. This rule was found to be 96% sensitive and 62% specific at predicting serious short term outcome, and if applied to the derivation cohort, would have decreased hospital admissions by 10%. This group has not yet prospectively validated their

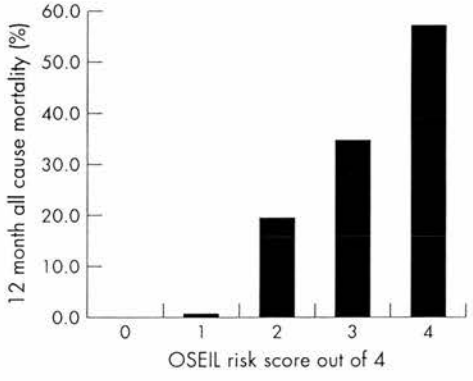

Figure 2 Rates of 12 month, all cause mortality according to the OESIL score in the derivation cohort. Reprinted from Colivicchi F *et al*,[40] with permission from Oxford University Press.

rule; however, two other studies have attempted to do so.[42 43] Sensitivity in both studies was much lower than in the derivation cohort of Quinn *et al* (52% *v* 91%), in one study missing 26 of the 50 patients who had a serious outcome.[42] An attempt has also been made to validate the rule for long term (1 year) mortality with a sensitivity of 88% and specificity of 56% in 658 ED attendees.[44]

With underlying cardiac failure being associated with a poor prognosis in syncope, clinical decision rules utilising biochemical markers of cardiac failure severity (C-reactive protein or brain natriuretic peptide)[45–48] may prove useful in the future. As yet, these have not been studied.

Guidelines

The ACP guidelines of 1997[37 38] reviewed all existing literature in order to provide guidelines on diagnosing syncope. They included guidance on which patients with unexplained syncope should be admitted to hospital, and divided patients into groups depending on the apparent risk of adverse outcome. Three main groups were identified. High risk patients in whom admission was indicated were those with a history of coronary artery disease, congestive cardiac failure (CCF) or ventricular tachycardia, those with accompanying symptoms of chest pain, those with physical signs of CCF, significant valve disease, stroke or focal neurology, and patients with ECG findings of ischemia, dysrhythmia (serious bradycardia or tachycardia), long QT interval, or bundle branch block.

The second group identified were those in whom they felt admission was often indicated. This "intermediate risk" group included patients with a sudden loss of consciousness with injury, tachycardia, or exertional syncope, those with frequent episodes (which lead to an increased likelihood of injury but are not associated with an increased mortality), those with a suspicion of coronary heart disease or dysrhythmia, moderate to severe postural hypotension, and those aged >70 years.

A third "low risk" group was defined as those who do not fall into either of the above groups. These patients may be discharged with or without outpatient follow up. Thakore *et al* showed that adherence to these guidelines in their UK ED population, would have increased hospital admissions by 38–58%.[4]

While other guidelines have followed,[16 17] none have been prospectively validated. All guidelines include history, examination and investigation of syncopal patients, however only the American College of Emergency Physicians (ACEP) guidelines have focused directly on ED investigations and management.[49] These suggest admission for patients with a history of congestive heart failure or ventricular dysrhythmias, associated chest pain or other symptoms compatible with acute coronary syndrome, evidence of significant congestive heart failure or valvular heart disease on physical examination, or ECG findings of ischemia, dysrhythmias, prolonged QT interval, or bundle branch block.

The ACEP guidelines also suggest that admission should be considered for patients with syncope who are older than 60 years, have a history of coronary artery or congenital heart disease, have a family history of unexpected sudden death, or in younger patients who present with exertional syncope without an obvious benign aetiology. Presently it is unclear whether either the application of guidelines to syncope management or the practice of admitting patients with syncope to hospital has any impact on patient outcome. No such benefits have ever been demonstrated.

CONCLUSIONS

Identifying a cardiac cause for syncope is a poor prognostic indicator for ED patients presenting with syncope. This is related to the severity of the patient's underlying cardiac disease rather than the syncopal event itself. Patients presenting with syncope who have significant cardiac disease should be investigated thoroughly to determine the nature of the underlying heart disease and the cause of syncope. At present however, there is little evidence that this improves their dismal prognosis (>30% 1 year mortality).

There are five small risk stratification studies on syncope in the ED.[7 8 29 40 41] All five used different characteristics and outcome measures in their risk stratification tools. Only two were prospective and had mixed results.[29 40] None have been examined in a UK population.

Presently the ACEP guidelines[49] are the most useful aids to the management of syncope in the ED; however, the OESIL score[40] may be a useful ED risk stratification tool.

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ORIGINAL ARTICLE

The Risk stratification Of Syncope in the Emergency department (ROSE) pilot study: a comparison of existing syncope guidelines

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Aims: This study was conducted as a feasibility pilot for the Risk stratification Of Syncope in the Emergency department (ROSE) study. The secondary aim was to compare the performance of our existing emergency department (ED) guidelines with existing clinical decision rules (Osservatorio Epidemiologico sulla Sincope nel Lazio (OESIL) Score and San Francisco Syncope Rule; SFSR) at predicting short-term (1 week and 1 month) and medium-term (3 months) serious outcomes for patients with syncope presenting to the ED.

Methods: This was a prospective cohort study. All patients presenting with syncope aged ⩾16 years between 7 November 2005 and 7 February 2006 were prospectively enrolled.

Results: 99 patients were recruited over a 3-month period. 44 patients were admitted and 55 discharged from the ED. 11 patients had a serious outcome: 8 by 7 days and a further 3 by 3 months. Five patients died by 3 months and six others had an alternative serious outcome. All 11 patients had been admitted from the ED, 7 were at high risk, 4 were at medium risk and none were at low risk according to our existing ED guidelines. Percentages of serious outcomes were 0%, 2.9%, 8.0%, 22.7% and 37.5% for OESIL scores of 0, 1, 2, 3 and 4 respectively. 40 patients had none of the 5 SFSR high-risk factors (0 serious outcomes = 0%) and 59 patients had an SFSR high-risk factor (11 serious outcomes = 18.6%). The risk of serious outcome at 7 days, 1 month and 3 months was 8.1%, 8.1% and 11.1%, respectively.

Conclusions: A study to derive and validate a UK ED syncope clinical decision rule is feasible. This pilot study has evaluated the OESIL score, the SFSR and our existing ED guidelines, and has shown that each is able to identify an increased probability of medium-term serious outcome in patients with syncope. The SFSR shows good sensitivity at the expense of an increase in admissions to hospital; however, our existing ED syncope guidelines and the OESIL Score, although being able to successfully risk stratify patients, are not sufficiently sensitive to be able to reduce admissions without missing patients at risk of a serious outcome. Undoubtedly there is a need for a simple UK-derived clinical decision rule for patients presenting with syncope to enable safe, effective clinical care and to aid less experienced decision makers.

Syncope is a transient loss of consciousness with an inability to maintain postural tone followed by a spontaneous recovery.[1] It accounts for 3% of emergency department (ED) visits and 1–6% of hospital medical admissions, affecting 6 per 1000 people per year.[2 3] Clinical assessment of syncope is difficult owing to the heterogeneous nature of underlying causes, ranging from benign neurocardiogenic syncope to potentially fatal arrhythmias.

In 1983, Kapoor *et al*[4] published the first prospective syncope study. The 12-month mortality was 14%. Mortality was greatest in patients in whom a cardiovascular cause was identified (30%). Subsequent studies have shown that underlying heart disease in patients with syncope is associated with a poor prognosis.[5] Recent emphasis has focused on risk stratification of patients with syncope. Although guidelines have been issued,[6–10] evidence with respect to ED management is sparse. There are five risk stratification studies.[11–16] All involved small numbers of patients and used different characteristics and outcome measures in their risk stratification tools. Only one study, US-based, looked at short-term adverse outcome,[15 16] which is relevant to emergency medicine practice. No studies have been examined in a UK population.

With growing pressures on acute medical beds and an increasingly elderly population, a large study of this common presenting symptom is needed to identify high-risk populations requiring further investigation and low-risk patients who may be discharged safely. Accurate identification of patients would enable specific targeting of resources and prevent excessive investigation of patients with benign causes.

This study was conducted as a pilot for the Risk stratification Of Syncope in the Emergency department (ROSE) study. The primary aim was to demonstrate the feasibility of study recruitment and to test the study method before the main ROSE study. The secondary aim was to compare the performance of existing clinical decision rule (CDRs; The Osservatorio Epidemiologico sulla Sincope nel Lazio (OESIL) score and San Francisco Syncope Rule (SFSR)) with our existing departmental syncope guidelines (based on the European Society of Cardiology,[9 10] the American College of Physicians (ACP)[6 7] and the American College of Emergency Physicians guidelines[8]; table 1) to predict short-term (7 days and 1 month) and medium-term (3 month) serious outcomes for patients with syncope presenting to a UK ED.

Abbreviations: ACP, American College of Physicians; CDR, clinical decision rule; ED, emergency department; EPR, electronic patient record; ROSE, Risk stratification Of Syncope in the Emergency department; OESIL, Osservatorio Epidemiologico sulla Sincope nel Lazio; SFSR, San Francisco Syncope Rule

Table 1 Our emergency department's existing syncope guidelines based on the European Society of Cardiology,[9 10] American College of Physicians[6 7] and American College of Emergency Physicians guidelines[8]

High risk (admit)	Medium risk (consider discharge with early outpatient review)
History findings	
Palpitations related to syncope	Age >60 years
Associated chest pain	No prodromal symptoms
Associated headache	Previous myocardial infarct
Related to exertion	Known history of valvular heart disease
Family history of sudden death at <60 years	Known angina/coronary artery disease
Previous history of VT/VF/cardiac arrest	Known history of congestive cardiac failure
Examination findings	
Systolic heart murmur heard	>20 mm Hg drop on standing
Signs of heart failure present	Diastolic heart murmur heard
Systolic BP <90 mm Hg	Ventricular pause >3 s on carotid sinus massage
Suspicion of pulmonary embolism	Trauma associated with collapse
AAA detected	
New neurological signs on examination	
Suspicion of CVA or SAH	
FOB present on PR	
Other suspicions of GI bleed	
ECG findings	
Mobitz type II heart block	Right bundle branch block
Wenkebach heart block	QRS duration >120ms
Bifascicular block	Old T wave/ST segment changes
Complete heart block	Frequent pre-excited QRC complexes
Sinus pause >3 s	Q waves unchanged from old ECG
New ST elevation ventricular tachycardia	Atrial fibrillation or flutter
Sinus bradycardia <50	PR >200 ms (first-degree heart block)
Sinoatrial block	
QTc >450 ms	**Low risk (consider discharge)**
NEW T wave/ST segment changes	None of the above characteristics
Brugadas (ST segment elevation V1–V3)	
Arrhythmogenic right ventricular dysplasia	

AAA, abdominal aortic aneurysm; BP, blood pressure; CVA, cerebrovascular accident; FOB, faecal occult blood; GI, gastrointestinal; PR, rectal examination; SAH, subarachnoid haemorrhage; VF, ventricular fibrillation; VT, ventricular tachycardia.

METHODS

Setting

The ED of the Royal Infirmary of Edinburgh, UK (85 000 adult attendances per annum).

Inclusion criteria

All patients presenting with syncope aged ⩾16 years between 7 November 2005 and 7 February 2006 were prospectively enrolled into the study.

Exclusion criteria

Patients aged <16 years, those previously recruited and those with a history of seizure with prolonged post-ictal phase were excluded. Patients who were unable to give either written or verbal informed consent were also excluded.

Enrolment into study

ED nurses identified potentially eligible patients and a data collection form was placed with the patient's records. The treating doctor was responsible for deciding whether the patient had had an episode of syncope after the initial assessment. All doctors involved in the study had undergone a 15-min training session on criteria associated with a diagnosis of syncope. A decision to enrol a patient was not overturned later by the study team and enrolled patients were analysed on an intention-to-treat basis. The study team reviewed the notes of any patient who had been initially flagged by the triage nurse, but later rejected by the doctor. Only nine patients were rejected in this manner. Reasons for the doctor rejecting a patient were inability to obtain consent, patients being found collapsed for an unknown period of time or patients presenting with a likely seizure.

Assessment

All patients underwent a standardised assessment using 31 predetermined variables (11 focused on clinical features, 9 on medical history and 11 on current medication), 28 examination variables and 26 ECG variables. These were selected after careful systematic review of the literature to identify characteristics previously shown to be associated with serious outcome. After a full history and examination, all patients underwent a 12-lead ECG, lying and standing blood pressures were recorded and a "BM stix" glucose estimation. Patients who were at medium or high risk according to our ED's existing syncope guidelines also had full blood count, urea, creatinine, glucose, electrolytes and C reactive protein measured. Patients still in the ED at 12 h were defined as admitted. Patients were admitted, referred to medical outpatient departments or discharged according to our ED's existing syncope guidelines, and a study information form was completed. Patients admitted to the hospital or who attended the medical outpatient department underwent evaluations for any clinical or historical findings suggestive of a cause of syncope at the discretion of the treating consultant, including 24-h ECG tape and echocardiography investigations.

Endpoint measures

Primary end point was a serious outcome at 1 week, 1 month and 3 months. Serious outcomes were predefined and were all-cause death, acute myocardial infarction (history of chest

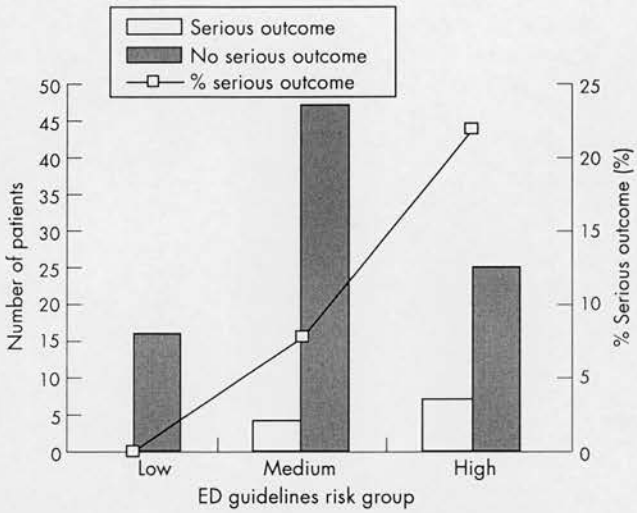

Figure 1 The number of patients from each emergency department (ED) guidelines risk group for serious and not serious 3-month outcomes, and percentage of serious outcome for each ED guidelines risk group.

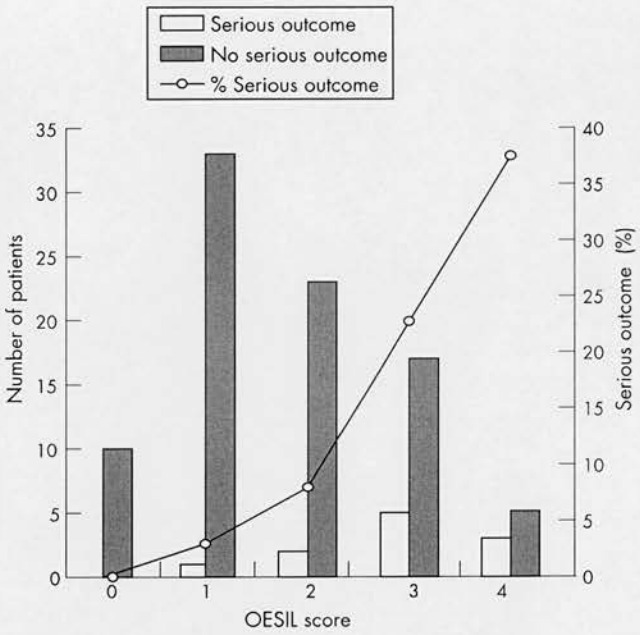

Figure 2 Graph showing number of patients with each Osservatorio Epidemiologico sulla Sincope nel Lazio (OESIL) score for serious and not serious 3-month outcomes, and percentage of serious outcome for each OESIL score.

pain or ECG changes and troponin I >2), life-threatening arrhythmia (documented on monitor or ECG during inpatient stay or on outpatient Holter monitoring and requiring treatment), pulmonary embolus (confirmed on ventilation perfusion lung scan/CT pulmonary angiography and requiring treatment), cerebrovascular accident/subarachnoid haemorrhage (CT or lumbar puncture diagnosis), haemorrhage requiring a blood transfusion of two units or more during inpatient stay and an acute surgical procedure or endoscopic intervention secondary to a suspected cause of syncope.

Once 3 months had elapsed after ED attendance for all patients, the hospital computer system was interrogated to see whether the patients had returned to any hospital in the Lothian region. The hospital records were acquired and scrutinised for all patients who had attended the ED or outpatient department or who had been admitted as inpatients. All deceased patients were identified via the hospital computer system, which is directly linked with the national death register and primary care patient records. Hospital notes were scrutinised to determine whether each patient with syncope had had a serious outcome within 3 months of their attendance to the ED. All patients could be followed up, and all hospital notes and records could be traced. For any patient residing outside the Lothian region, either their general practitioner or the patient was contacted.

The presence or absence of an SFSR high-risk factor and the patient's OESIL score was determined by the study team from specifically prospectively acquired information on the data collection form. The OESIL score is based on four characteristics: age >65 years, a clinical history of cardiovascular disease, syncope without prodromal symptoms and an abnormal ECG. The presence of each characteristic scores one. One-year mortality has been shown to increase with increasing score.[13] The SFSR defines high-risk patients as those having any one of the five risk factors: abnormal ECG (non-sinus rhythm or new abnormality), anaemia (haematocrit <30%), a complaint of shortness of breath, systolic hypotension (<90 mm Hg) and a history of congestive cardiac failure.[15 16] The patient's ED guideline risk group (high, medium and low) was determined by the study doctor after an initial assessment.

Review of missed patients

To determine the recruitment rate of patients into the study, a retrospective search of all ED electronic patient records (EPRs) between 7 November 2005 and 7 February 2006 was conducted looking for the keywords "syncope", "collapse", "faint", "loss of consciousness" or "loc" appearing anywhere on the EPR. All EPRs with one of these terms were then hand searched and a decision was made from the notes whether the patient fitted the study's inclusion criteria. A list was compiled of all patients who fitted the study inclusion criteria, along with their demographic details, and compared using Chi-squared and Mann-Whithey U tests with those patients who had been enrolled into the study.

Statistical analysis

All patient data were entered into a specially designed Microsoft Access database and exported into Excel for statistical analysis. A power calculation was not performed for the pilot study; however, it was decided that 100 patients would be sufficient for the primary aim. Sensitivity, specificity, predictive values and likelihood ratios were calculated for existing CDRs, current ED guidelines and some selected patient characteristics, and serious and non-serious outcome groups were compared using Fisher's exact test (table 2).

RESULTS

Ninety-nine consecutive adult patients were recruited over a 3-month period between 7 November 2005 and 7 February 2006. It was thought that 100 patients had been enrolled; however, one patient episode had been erroneously duplicated during data entry. In all, 44 patients were admitted to the hospital and 55 were discharged from the ED. Of the 11 patients with a serious outcome, 8 had developed this by 7 days and 3 further patients had developed a serious outcome by 3 months. In all, therefore, 11 patients had a serious outcome by 3 months. Of these, five patients died and six had an alternative serious outcome. All 11 had been admitted to hospital from the ED. The percentage risk of serious outcome at 7 days, 1 month and 3 months was 8.1%, 8.1% and 11.1%, respectively.

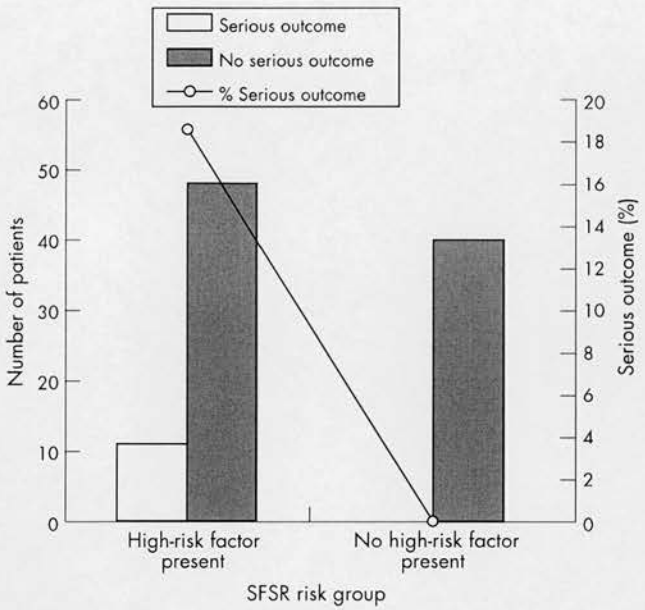

Figure 3 The number of patients with each San Francisco Syncope Rule (SFSR) risk group for serious and not serious 3-month outcomes, and percentage of serious outcome for each SFSR risk group.

Current ED guidelines

In all, 32 patients were at high risk, 51 at medium risk and 16 at low risk according to our existing ED guidelines. Of the patients with a serious outcome, seven were at high risk, four were at medium risk and none was at low risk. A total of 7 of 32 (22%) high-risk patients, 4 of 51 (8%) medium-risk patients and 0 of 16 (0%) low-risk patients had a serious outcome (fig 1). In all, 19 of the 51 medium-risk patients were admitted to hospital and no patient with a subsequent serious outcome was discharged directly from the ED. Admission of all high-risk patients only (by ED guidelines) would have led to 12 fewer admissions; however, 4 patients with serious outcomes would have been discharged. Admission of all medium- and high-risk patients only would have led to 39 further admissions but would have detected all patients with serious outcomes.

OESIL score

A total of 10 patients had an OESIL score of 0 (no serious outcomes), 34 had an OESIL score of 1 (1 serious outcome), 25 had an OESIL score of 2 (2 serious outcomes), 22 had an OESIL score of 3 (5 serious outcomes) and 8 patients had an OESIL score of 4, of which 3 had a serious outcome (fig 2).

Percentages of serious outcomes were 0%, 2.9%, 8%, 22.7% and 37.5% for OESIL scores of 0, 1, 2, 3 and 4, respectively (fig 2). This compares with 0%, 0.8%, 19.6%, 34.7% and 57.1% for 12-month mortality in Colivicchi *et al*'s[13] paper. Use of the OESIL score with a cut-off for admission of an >0 instead of existing guidelines would have led to 55 further admissions, with no patients having serious outcomes being discharged. An OESIL score >1 would have led to 11 further admissions, with 1 patient having a serious outcome being discharged. An OESIL score >2 would have led to 14 fewer admissions, with 3 patients having serious outcomes being discharged and an OESIL score >3 would have led to 36 fewer admissions, with 8 patients having serious outcomes being discharged.

San Francisco Syncope Rule

A total of 40 patients had none of the 5 SFSR risk factors (with no serious outcomes = 0%) and 59 patients had an SFSR high-risk factor present (11 serious outcomes = 18.6%; fig 3). Use of the SFSR instead of existing guidelines would have led to 15 further admissions, with no improvement in sensitivity on current practice in our ED.

Study pick-up rate and comparison of study group and "missed" group

A total of 263 patients presenting between 7 November 2005 and 7 February 2006 were identified from the EPR search as fitting the study's inclusion criteria. The study therefore managed to pick up 37.6% of patients eligible for inclusion. There were 74 men (45%) and 90 women in the "missed group" compared with 48 men (48%) and 51 women in the "study group" ($p = 0.6$, NS, χ^2 test). Neither the ages of the study group nor of the missed group were normally distributed. The median age of the study group was 71 years (interquartile range (IQR) 47–81) and that of the missed group was 62.5 years (IQR 29–78; $p = 0.047$, significant at the 5% level, Mann–Whitney U test).

DISCUSSION

This study was conducted as a pilot for the ROSE study. It is the first prospective study on syncope within UK ED practice and the first attempt to evaluate existing clinical decision rules in the UK. The primary aim of the study was to assess the process of patient recruitment and to test the study method and feasibility of data collection before the main ROSE study.

A power calculation was not performed before the pilot, and we acknowledge that the study did not enrol a cohort of patients large enough to derive a clinical decision rule, one of the aims of the main ROSE study. The secondary aim of the study was to compare the performance of our current ED guidelines with the OESIL score and the SFSR at predicting short- and medium-term serious outcomes. Again, because of the small size of the study, we have only conducted a statistical analysis of serious outcome at 3 months. The findings of this pilot study, although requiring cautious interpretation, are important.

This study only recruited 37.6% of eligible patients. Conducting ED research such as this is difficult; however, the recruitment rate will need to be improved for the main study. Closer analysis reveals that the "missed" group had a lower median age than the "study" group and that the distribution of risk groups in the "study" group is skewed towards the more serious end of the scale. This suggests that the treating doctors were not enrolling younger patients with simple low-risk vasovagal faints. This has probably led to a higher serious outcome rate. If this is repeated in the main study, it may mean that any derived clinical rule may not be applicable to this group, albeit a low-risk one. This problem must therefore be addressed in the main study by further training of recruiters and an improved method of picking up all eligible patients.

Using a 7-day event rate of 10%, a power calculation performed to determine sample size requirements for a large prospective derivation and a validation study suggested that 500 patients would need to be recruited into a derivation cohort and 500 into a validation cohort. With improvements in our recruitment processes, we estimate that this is feasible over 2 years.

There are few studies on syncope based on in UK EDs. In 1999 Thakore *et al*[17] looked at practice in one UK ED and showed that few patients had relevant syncope symptoms documented or an ECG recorded. In all, 28% of patients with an abnormal ECG and 40% with a history of organic heart disease were sent home from the ED. Prior to our study, the only UK ED study of syncope outcome was conducted by Crane.[18] This retrospective study of 210 patients presenting during an 8-week

Table 2 Sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio and p value of emergency department guidelines, Osservatorio Epidemiologico sulla Sincope nel Lazio Score, San Francisco Syncope Rule and some selected characteristics

	PPV	NPV	Sensitivity	Specificity	PLR	NLR	p Value
High-risk group (based on ED guidelines)	0.219	0.940	0.636	0.716	2.239	0.508	0.035*
High- or medium-risk group (based on ED guidelines)	0.133	1.000	1.000	0.182	1.222	0	0.203
One of SFSR risk factors present	0.186	1	1	0.455	1.835	0.000	0.006*
OESIL >0	0.124	1.000	1.000	0.114	1.128	0.000	0.597
OESIL >1	0.182	0.977	0.909	0.489	1.778	0.186	0.011*
OESIL >2	0.267	0.957	0.727	0.750	2.909	0.364	0.003*
OESIL >3	0.375	0.912	0.273	0.943	4.800	0.771	0.426
Abnormal ECG	0.158	0.952	0.818	0.455	1.500	0.400	0.111
History of CV disease	0.222	0.931	0.545	0.761	2.286	0.597	0.065
Age >65 years	0.190	1	1	0.466	1.872	0	0.002*
History of CCF	0.500	0.897	0.091	0.989	8	0.920	0.211

CCF, congestive cardiac failure; CV, cardiovascular; ED, emergency department; Hx, history; NLR, negative likelihood ratio; NPV, negative predictive value; OESIL, Osservatorio Epidemiologico sulla Sincope nel Lazio; PLR, positive likelihood ratio; PPV, positive predictive value; SFSR, San Francisco Syncope Rule.
*Significant at the 5% level, Fisher's exact test.

period showed that it was possible to stratify UK ED patients with syncope according to ACP guidelines.[6 7] Patients in ACP group 1 (high risk) had a 1-year mortality of 36%, compared with patients assigned to ACP group 2 (intermediate risk; 14%) and to ACP group 3 (low risk; 0%). Our study confirms the findings of Crane, showing that our ED guidelines (based on the European Society of Cardiology,[9 10] ACP[6 7] and the American College of Emergency Physician guidelines[8]) can successfully risk stratify UK ED patients with syncope.

Following our existing ED guidelines and making a decision to admit a high-risk patient with a "high-risk" factor led to a reasonable sensitivity (0.636) and good specificity (0.716) for serious outcome. Considering admission for all medium- and high-risk patients ensures that no serious outcomes are missed; however, this would lead to a large increase in admissions for only a small increase in the detection of patients with serious outcomes. Despite our guidelines suggesting that medium-risk patients could be considered for discharge to outpatient review, 19 of the 51 medium-risk patients were admitted to hospital and no patients with serious outcomes were discharged. This suggests that the doctor's judgement may have played an important part in deciding which medium-risk patients may have been at increased risk. If they have not already, all UK EDs should have similar guidelines in place in order to effectively risk stratify patients presenting with syncope.

The OESIL score was originally derived and validated to predict 12-month all-cause mortality. It differs from the SFSR in that the original study demonstrated that an increasing OESIL score is associated with an increased risk of a serious outcome, whereas the SFSR relies only on the presence of one of five high-risk factors. Our study findings are similar to those of the original study; however, where to place the cut-off for admission to hospital is unclear and was not defined in the original study. Admitting patients who have an OESIL score >1 has the required sensitivity, but would have led to 11 more admissions. Setting a higher cut-off is associated with an improved specificity at the expense of a reduced sensitivity.

The SFSR was originally devised to predict a 7-day serious outcome. Again, our study findings are similar to the results of the original study, the SFSR showing a sensitivity of 1 and a specificity of 0.455. Adopting this rule, however, would have led to 15 more admissions with the detection of no more serious outcomes. This suggests that although the SFSR may be a sensitive tool in the UK ED population, its use would increase admissions with only a small increase in the detection of patients with serious outcome. It is interesting that the OESIL risk factor "age >65" alone performs better than both the SFSR and our existing ED guidelines.

Clearly, there is a need for a large prospective study of syncope in the UK ED population. Existing CDRs show some promise; however, there is room to improve these tools. There are large differences in practice and admission policies between UK and North American EDs and therefore there is a definite need to derive and validate a more useful tool for use in the UK population. Despite this being costly and time consuming its potential benefits are many, including reducing unwarranted admissions, improving patient outcome and satisfaction and allowing resources to be concentrated on patients most at risk of adverse events.

CONCLUSION

This pilot demonstrates that a study to derive and validate an ED syncope stratification rule is feasible. The pilot also enabled the study method and data collection process to be assessed and revised before starting the main ROSE study.

This study has evaluated the OESIL score, the SFSR and our existing ED guidelines, and has shown that each is able to identify an increased probability of medium-term serious outcome in patients with syncope despite the OESIL score being initially derived and validated for long-term prediction and the SFSR for short-term outcome. The SFSR shows good sensitivity at the expense of an increase in admissions to hospital; however, our existing ED syncope guidelines and the OESIL score, although being able to successfully risk stratify patients, are not sufficiently sensitive to be able to reduce admissions without missing patients who later go on to develop a serious outcome.

Undoubtedly, there is a need for a simple UK-derived clinical decision rule for patients presenting with syncope to enable safe, effective clinical care and to aid less experienced decision makers.

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ORIGINAL ARTICLE

Role of brain natriuretic peptide (BNP) in risk stratification of adult syncope

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Aims: To assess the value of a near-patient brain natriuretic peptide (BNP) test to predict medium term (3 month) serious outcome for adult syncope patients presenting to a UK emergency department (ED).

Methods: This was a prospective cohort pilot study. Consecutive patients aged ≥16 years presenting with syncope over a 3 month period were eligible for prospective enrolment. All patients who were medium or high risk according to our ED's existing syncope guidelines underwent near-patient BNP testing using the Triage point of care machine.

Results: 99 patients were recruited. 72 of 82 high and medium risk patients underwent BNP measurement. 11 patients had a serious outcome, 9 of whom had BNP measured. In 25 (35%) patients, BNP was ≥100 pg/ml, and in 3 of these it was >1000 pg/ml. 6 of the 25 patients (24%) with a BNP >100 pg/ml, and all 3 patients with a BNP >1000 pg/ml, were in the serious outcome group. BNP was raised over 100 pg/ml in 6 of the 9 serious outcome patients having a BNP measured (66%), and over 1000 pg/ml in 3 (33%).

Conclusions: This early work suggests that BNP may have a role in the risk assessment of syncope patients in the ED. Further work is required to see how BNP interacts with other clinical variables. Near-patient BNP testing may be shown to be an independent predictor of adverse outcome either alone or incorporated into existing syncope clinical decision rules and scores in order to improve their sensitivity and specificity. Further studies are required to evaluate this.

Syncope is a transient, self limited loss of consciousness usually leading to falling.[1] It accounts for 3% of emergency department (ED) visits and 1–6% of hospital medical admissions, affecting 6 per 1000 people per year.[2 3] In 1983, Kapoor *et al*[4] published the first prospective syncope study showing a 12 month mortality of 14%. Mortality was greatest in patients in whom a cardiovascular cause was identified (30%). Subsequent studies have shown that underlying heart disease in patients with syncope is associated with a poor prognosis.[5]

Recent emphasis has focused on risk stratifying syncope patients. With growing pressures on acute medical beds and an increasingly elderly population, there is a need to identify high risk populations requiring further investigation, and low risk patients who may be discharged safely. Accurate identification of such groups would enable specific targeting of resources and prevent excessive investigation of patients with benign causes of syncope. No risk stratification studies have yet investigated the role of biochemical markers in risk stratification.

Brain (or B-type) natriuretic peptide (BNP), which is secreted in response to an increase in ventricular volume and pressure load, is known to be an excellent marker of prognosis in patients with heart failure or cardiac disease.[6 7] As previously mentioned, it is well established that prognosis in syncope is related to the presence of underlying heart disease,[5] and all existing syncope clinical decision rules include either a history of congestive heart failure[8–11] or of underlying cardiac disease.[12 13] Tanimoto *et al* in 2004 conducted the only syncope study to date that has utilised BNP.[14] This study evaluated the usefulness of BNP to separate cardiac and non-cardiac causes of syncope. The investigators retrospectively evaluated 148 consecutive syncope patients admitted to hospital; 61 of these patients were found to have a cardiac cause for their syncope. A BNP value of ≥40 pg/ml was found to be 82% sensitive and 92% specific for identifying cardiac syncope.

We therefore hypothesised that BNP could be an excellent ED marker of medium term (3 month) syncope outcome. The aim of this pilot study was to assess the value of a near-patient BNP test to predict medium term (3 month) serious outcome for syncope patients presenting to a UK ED, and to compare the performance of BNP with our existing departmental syncope guidelines (table 1) based on the European Society of Cardiology,[1 15] the American College of Physicians,[16 17] and the American College of Emergency Physicians guidelines.[18]

METHODS

Setting

The ED of the Royal Infirmary of Edinburgh (85 000 adult attendances per annum).

Inclusion criteria

Consecutive patients presenting with syncope aged 16 years or over between 7 November 2005 and 7 February 2006 were eligible for prospective enrolment. Syncope was defined as a transient loss of consciousness with an inability to maintain postural tone, followed by a spontaneous recovery without need for therapeutic or electrical intervention. Data from this same patient cohort were used to compare our existing ED guidelines with the San Francisco Syncope Rule[10 11] and the OESIL score,[13] and has been published previously.[19]

Exclusion criteria

Patients under 16 years of age, those previously recruited, and those having a history of seizure with prolonged post-ictal phase were excluded. Patients who were unable to give either written or verbal informed consent were also excluded.

Abbreviations: BNP, brain natriuretic peptide; CT, computed tomography; ECG, electrocardiogram; ED, emergency department; EPR, electronic patient records; IQR, interquartile range

Table 1 Our existing emergency department syncope guidelines based on the European Society of Cardiology,[1 15] the American College of Physicians,[16 17] and the American College of Emergency Physicians guidelines[18]

High risk (admit)	Medium risk (consider discharge with early outpatient review)
History findings	*History findings*
• Palpitations related to syncope	• Age >60 years
• Associated chest pain	• No prodromal symptoms
• Associated headache	• Previous myocardial infarct
• Related to exertion	• Known history of valvular heart disease
• Family history of sudden death <60	• Known angina/coronary artery disease
• Previous history of VT/VF/cardiac arrest	• Known history of congestive cardiac failure
Examination findings	*Examination findings*
• Systolic heart murmur heard	• >20 mm Hg drop on standing
• Signs of heart failure present	• Diastolic heart murmur heard
• Systolic BP <90 mm Hg	• Ventricular pause >3 s on carotid sinus massage
• Suspicion of pulmonary embolism	• Trauma associated with collapse
• AAA detected	
• New neurological signs on examination	*ECG findings*
• Suspicion of CVA or SAH	• Right bundle branch block
• FOB present on PR exam	• QRS duration >120 ms
• Other suspicions of GI bleed	• Old T wave/ST segment changes
	• Frequent pre-excited QRS complexes
ECG findings	• Q waves unchanged from old ECG
• Mobitz type II second degree heart block	• Atrial fibrillation or flutter
• Mobitz type I (aka Wenkebach) second degree heart block	• PR >200 ms (1st degree heart block)
• Bifascicular block	
• Complete heart block	**Low risk (consider discharge)**
• Sinus pause >3 s	• None of the above characteristics
• New ST elevation	
• VT	
• Sinus bradycardia <50	
• Sinoatrial block	
• QTc >450 ms	
• New T wave/ST segment changes	
• Brugada syndrome (ST segment elevation V1–V3)	
• Arrhythmogenic right ventricular dysplasia	

AAA, abdominal aortic aneurysm; BP, blood pressure; CVA, cerebrovascular accident; ECG, electrocardiogram; FOB, faecal occult blood; GI, gastrointestinal; PR, per rectum; SAH, subarachnoid haemorrhage; VF, ventricular fibrillation; VT, ventricular tachycardia.

Study enrolment

Eligible patients were flagged at the ED high dependency triage area and a data collection form was placed in the patient's records. The treating doctor was responsible for deciding eligibility. Assessment of patients was carried out by routine ED clinical staff. A decision to enrol a patient was not overturned later by the study team and enrolled patients were analysed on an intention to treat basis. Written consent was obtained from all enrolled patients. This study received ethical approval from Lothian's Regional Ethical Committee.

Assessment

All patients underwent a standardised assessment using 31 predetermined variables (11 focused on clinical features, 9 on past medical history, and 11 concerning current medication), 28 examination variables and 26 electrocardiogram (ECG) variables. After a full history and examination, all patients who were medium or high risk according to our ED's existing syncope guidelines also had near-patient BNP testing. BNP was measured using a whole blood immunoassay technique utilising the Triage point of care machine. Treating physicians were not blinded to the result of the BNP test. Admitted patients also underwent a laboratory based troponin I at least 12 h post-syncope at the discretion of the admitting team. Patients were admitted, referred to medical outpatients, or discharged according to our ED's existing syncope guidelines and a study data collection form was completed for each patient.

End point measures

The primary end point was serious outcome at 3 months. Serious outcomes were pre-defined and were all cause death, acute myocardial infarction (history of chest pain or ECG changes and troponin I >2.0), life threatening arrhythmia (documented on monitor or ECG during inpatient stay or on outpatient Holter monitoring, and requiring treatment), pulmonary embolus (confirmed on ventilation perfusion scan (VQ) or CT pulmonary angiography scan (CTPA), and requiring treatment), cerebrovascular accident/subarachnoid haemorrhage (CT or lumbar puncture diagnosis), haemorrhage requiring a blood transfusion of 2 units or more during inpatient stay, and an acute surgical procedure or endoscopic intervention secondary to a suspected cause of syncope.

Once 3 months had elapsed following ED attendance, the hospital computer system was interrogated to see whether each patient had returned to any hospital in the Lothian region. The hospital records were reviewed for all patients who had attended the ED or outpatient department or who had been admitted as an inpatient. Any deceased patient in the Lothian region was also able to be identified via the hospital computer system and hospital records were acquired.

Hospital notes were reviewed to determine whether each patient had had a serious outcome within 3 months of their attendance to the ED with syncope. All patients were followed up. Two recruited patients from outside Lothian were contacted by phone. Hospital notes were available for all patients.

Table 2 Description of the 11 patients with a serious outcome

Patient study no.	Age	Sex	Serious outcome	Patient ESC risk	BNP pg/ml
7	68	M	Extreme bradycardia on 24 h tape including 2 pauses of 3.5 s and 4.0 s. Permanent pacemaker inserted. Alive at 3 months	Medium	461
17	71	M	Had AAA repair on day 1 with good recovery. Presented to the ED day 80 with leaking AAA repair. Died in theatre	High	–
24	90	F	Myocardial infarction (troponin 14.40). Also fast AF. Alive at 3 months	High	1340
32	67	M	Re-presented to the emergency department in cardiac arrest day 32. Unsuccessfully resuscitated. Primary cause unknown	High	2040
43	91	M	Ventricular standstill on ward. Permanent pacemaker inserted. Alive at 3 months	High	82.5
52	66	M	Died in hospital on day 79 after a hospital readmission. Cause not identified	High	26.5
55	76	M	Multiple episodes of ventricular tachycardia on ward. Internal defibrillator implanted. Alive at 3 months	High	–
59	76	M	2 episodes of ventricular standstill 7 s and 5 s each on 24 h tape. Diagnosis of episodic complete heart block made and permanent pacemaker inserted. Alive at 3 months	Medium	16.3
63	57	F	Died day 6 after index hospital admission. Syncope secondary to massive upper gastrointestinal haemorrhage. Patient also had terminal lung cancer	High	1040
66	74	M	Died day 6 after index hospital admission of left internal carotid artery thrombosis and left cerebral infarct. Also secondary right sided bronchopneumonia	Medium	144
78	81	F	Initial syncope thought secondary to hypotension. Interval 24 h tape showed episodes of fast AF and 5 prolonged pauses up to 3.6 s. Permanent pacemaker inserted. Alive at 3 months	Medium	489

AAA, abdominal aortic aneurysm; AF, atrial fibrillation; BNP, brain natriuretic peptide; ED, emergency department; ESC, European Society of Cardiology; F, female; M, male.

Review of missed patients

In order to determine the recruitment rate of patients into the study, a retrospective search was conducted of all ED electronic patient records (EPR) between 7 November 2005 and 7 February 2006 looking for the keywords "syncope", "collapse", "faint", "loss of consciousness" or "loc" appearing anywhere on the EPR. All EPRs with one of these terms were then hand searched and a decision was made from the notes whether the patient fitted the study's inclusion criteria. A list was compiled of all patients who fitted the study inclusion criteria but who had not been enrolled, along with their demographic details, and these were compared to those patients who had been enrolled into the study.

Statistical analysis

All patient data were entered into a specially designed Microsoft Access database and exported into Microsoft Excel for statistical analysis. Sensitivity, specificity, predictive values and likelihood ratios were calculated for BNP >100 pg/ml, BNP >1000 pg/ml and for current ED guidelines, and serious and non-serious outcome groups were compared using the Fisher exact test. The small sample size precluded calculation of receiver operator curves. The BNP cut off values of 100 pg/ml and 1000 pg/ml were decided before the study. The Triage point of care BNP assay defines any BNP value >100 pg/ml as an abnormal value. This value and a value 10-fold greater were arbitrarily chosen for analysis. This upper cut off was chosen as it was thought to be potentially high enough to be a possible rule-in value. A future larger study will attempt to define possible rule-in and rule-out levels using receiver operator curves.

The "study group" and the "missed group" were compared using the χ^2 test and the Mann–Whitney U test, and the "BNP group" and the "missed BNP" group were compared using the Fisher exact test.

RESULTS

Ninety-nine consecutive adult patients were recruited over a 3 month period between 7 November 2005 and 7 February 2006. It was thought that 100 patients had been enrolled; however, one patient episode had been erroneously duplicated

Table 3 Summary of results

	Serious outcome	No serious outcome	Total
Total patients	11 (11%)	88 (89%)	99
Admitted	11 (25%)	33 (75%)	44
Discharged	0 (0%)	55 (100%)	55
High risk group (based on ED guidelines)	7 (22%)	25 (78%)	32
Medium risk group (based on ED guidelines)	4 (8%)	47 (92%)	51
Low risk group (based on ED guidelines)	0 (0%)	16 (100%)	16
BNP not measured	2 (7%)	25 (93%)	27
BNP <100 pg/ml	3 (6%)	44 (94%)	47
BNP ≥100 pg/ml but <1000 pg/ml	3 (14%)	19 (86%)	22
BNP ≥1000 pg/ml	3 (100%)	0 (0%)	3

BNP, brain natriuretic peptide; ED, emergency department.

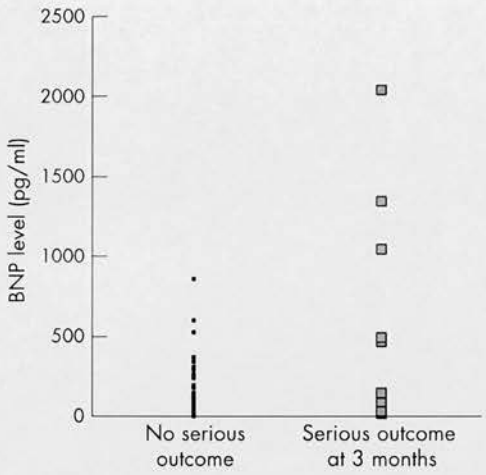

Figure 1 Relation between brain natriuretic peptide (BNP) level and outcome of study patients at 3 months.

during data entry. Forty-four patients were admitted to hospital and 55 were discharged from the ED. Eight of the 11 patients with a serious outcome had this by 7 days, and three further patients had developed a serious outcome by 3 months. In total, therefore, 11 patients (11.1%) had a serious outcome by 3 months. Of these, five patients had died and six others had an alternative serious outcome (table 2). All 11 had been admitted to hospital from the ED (table 3).

Seventy-two of the 82 medium and high risk patients had BNP measured, nine of whom had a serious outcome (12.5%) (fig 1). Those medium and high risk patients who did not undergo BNP measurement were missed because of either enrolling doctor error (seven patients) or BNP Triage point of care machine or operator error (three patients). The percentage serious outcome in those high and medium risk patients having BNP measured (72 patients) and the percentage serious outcome in the high and medium risk patients who did have BNP measured (10 patients) was not significantly different ($p = 0.617$, ns, Fisher exact test).

A BNP cut off of ⩾100 pg/ml was more sensitive than current ED guidelines for predicting medium term (3 month) serious outcome for syncope patients presenting to our ED (0.667 vs 0.636) with a similar specificity (table 4). A BNP cut off of ⩾1000 pg/ml had a specificity of 1 compared to that of 0.716 for current ED guidelines. While the BNP in two of these patients would have been unlikely to affect a decision to admit (acute myocardial infarction and massive upper gastrointestinal bleed both apparent on admission), in the third, there was no suspicion of likely poor outcome at the time of the patient's initial presentation to the ED.

Thirty of those admitted had troponin I measured, and only one of these was raised (14.40 ng/ml). This was thought to be due to an acute myocardial infarction. Of the 11 patients who developed a serious outcome, six had troponin measured and in only one was it raised.

A total of 263 patients presenting during the study period were identified from the EPR search as fitting the study's inclusion criteria. The study therefore enrolled 37.6% of patients eligible for inclusion. There were 74 men (45%) and 90 women in the "missed group", compared to 48 men (48%) and 51 women in the "study group" ($p = 0.60$, ns, χ^2). Neither the ages of the "study group" or "missed group" were normally distributed. Median age of the "study group" was 71.0 years (interquartile range (IQR) 47–81 years) and of the "missed group" was 62.5 years (IQR 29–78 years) ($p = 0.047$, significant at the 5% level, Mann–Whitney U test).

Table 4 Sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio and p value of selected characteristics

	PPV	NPV	Sensitivity	Specificity	+LR	−LR
BNP >100 pg/ml	0.240 (0.102 to 0.455)	0.936 (0.814 to 0.983)	0.667 (0.309 to 0.910)	0.698 (0.568 to 0.804)	2.211 (1.219 to 4.010)	0.477 (0.187 to 1.219)
BNP >1000 pg/ml	1.000 (0.310 to 1.000)	0.913 (0.814 to 0.964)	0.333 (0.090 to 0.691)	1.000 (0.928 to 1.000)	Inf (n/a)	0.667 (0.420 to 1.058)
High risk group (based on ED guidelines)	0.219 (0.099 to 0.404)	0.940 (0.847 to 0.981)	0.636 (0.316 to 0.876)	0.716 (0.608 to 0.804)	2.240 (1.284 to 3.907)	0.508 (0.230 to 1.120)

BNP, brain natriuretic peptide; ED, emergency department; +LR, positive likelihood ratio; −LR, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value. Confidence intervals in parentheses.

DISCUSSION

This is the first study that has looked at using biochemical markers to aid rapid risk stratification of patients presenting to the ED with syncope. There are currently several risk stratification scores[8–13] and also various guidelines to help the emergency physician decide who should be admitted for further investigation, and who could be safely discharged. Some of these rules have been derived to predict short term outcome (7 days) and some to predict longer term outcome (12 months).

We chose to look at a medium term (3 month) serious outcome. The goal of an ED risk stratification tool is to detect patients who are at risk of an imminent serious outcome, the course of which may be altered by early investigation, admission and intervention. A proportion of the short term (7 day) serious outcomes were expected to include such conditions as ruptured abdominal aortic aneurysms and subarachnoid haemorrhages. BNP is unlikely to be useful at predicting serious outcome in this non-cardiac syncope group. We also decided not to measure BNP in patients who were classified as low risk. This was because of the expected very low rate of serious outcome in this group.

Only one patient who had an adverse outcome had a raised troponin I at 12 h. This suggests that the good sensitivity that BNP shows for serious outcome is not due to it acting as a marker of myocardial ischaemia.

Patients who had been "missed" for inclusion into the study were statistically slightly younger compared to those enrolled into the "study" group. This is probably due to ED staff failing to enrol some younger syncope patients into the study. These patients would be more likely to be low risk and would therefore not have been eligible for BNP and troponin I testing. This difference is therefore unlikely to have biased the study findings.

This study shows that BNP may be a very useful predictor of serious outcome in syncope patients presenting to the ED. The advantage of the near-patient test is its immediate availability which makes it extremely useful for rapid ED decision making. BNP should now be included as a predictor variable in a large derivation and validation study of syncope to see if it is an independent predictor of adverse outcome and, if so, whether it has a role alone or as part of a clinical decision rule to aid the management of patients presenting with possible cardiac syncope to the ED. A power calculation suggests that 500 patients would be required in both the derivation and validation arms of such a study.

Conclusions

This early work suggests that BNP may have a role in the risk assessment of syncope patients in the ED. Further work is required to see how BNP interacts with other clinical variables. A BNP cut off of $\geq$100 pg/ml has a reasonable sensitivity for serious outcome, while a cut off of $\geq$1000 pg/ml has an excellent positive predictive value and specificity. Near-patient BNP testing may be shown to be an independent predictor of adverse outcome either alone or incorporated into existing syncope clinical decision rules and scores in order to improve their sensitivity and specificity. Further studies are required to evaluate this.

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The Prediction of Risk In Syncope using ECG characteristics (PRISE) pilot study: can heart rate variability be used to predict risk in patients presenting to the emergency department with syncope?

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ABSTRACT

Aim: This study was conducted as a feasibility pilot for the Prediction of Risk In Syncope using ECG characteristics (PRISE) study. The secondary aim was to determine whether heart rate variability (HRV) characteristics may be useful to distinguish low and high-risk syncope patients.

Methods: Adult patients presenting to the emergency department (ED) with syncope over a one-month period underwent a 5-minute 12-lead ECG. Study patients were assigned high, medium or low-risk status according to the ED's existing syncope guidelines as well as one of four likely diagnostic categories. ECG signals from all patients were then analysed and time domain HRV characteristics were derived using WelchAllyn's Cardioperfect interpretation software. A control group of patients was also recruited.

Results: Over a 4-week period in July 2007, 32 patients were recruited into the study group and 23 into the control group. ECG tracings of five study group patients were not suitable for analysis. According to the ED's existing syncope guidelines there were nine low-risk, 12 medium-risk and six high-risk patients with diagnostic categories as follows: postural hypotension, five; vasovagal, 16; cardiac, five and other, one. Patients with cardiac syncope had greater mean values for all HRV characteristics except NN number and NN minimum; however, with overlapping confidence intervals. Low-risk patients were more likely to be younger than medium and high-risk patients. No HRV parameters showed any significant differences.

Conclusions: Measuring HRV in the acute ED setting is feasible. If patients with cardiac and neurocardiogenic syncope have different HRV characteristics then it could be useful to determine a patient's underlying cause of syncope in the ED, which would allow earlier decision-making.

There are four main underlying diagnoses in patients presenting to the emergency department (ED) with syncope. Neurocardiogenic syncope accounts for approximately 40% of presentations, 25% will have orthostatic hypotension (primary or secondary), 10% will have a potentially life-threatening arrhythmia (ie, ventricular fibrillation, ventricular tachycardia, asystole) and 5% will have a structural cardiopulmonary problem (ie, pulmonary embolus, aortic stenosis or hypertrophic obstructive cardiomyopathy).[1]

Orthostatic hypotension can be quickly diagnosed with lying standing blood pressure measurements, and cardiopulmonary problems, although often subtle, may be detected from abnormalities present on physical examination. Currently, the methods used to distinguish neurocardiogenic syncope from life-threatening arrhythmias in ED patients include guidelines,[2-6] or the use of one of five available risk stratification tools.[7-12] None of these tools has yet demonstrated satisfactory accuracy when externally validated.[13] The ED clinician is therefore reliant on clinical judgement, often resulting in high rates of hospital admission.[14] Patients are frequently investigated further with 24-h tape and echocardiogram, which rarely elicit the underlying cause of the syncopal event.[5 6]

It is recognised that the human heart rate is not absolutely regular and undergoes cyclical variation mediated through the parasympathetic and sympathetic systems. The influence of the parasympathetic system occurs over a shorter period than the sympathetic system.

Heart rate variability (HRV) is a measure of the beat-to-beat variation between consecutive heartbeats. On a standard ECG, the maximum upwards deflection of a normal QRS complex is at the peak of the R wave and is termed the R point, and the time between two adjacent R points is the R–R interval. The ECG signal normally requires editing before HRV analysis can be performed (ie, correction for ectopic beats) after which the R points are termed N (normal) points. The normal-to-normal (N–N) interval is therefore the interval between adjacent QRS complexes resulting from sinus node depolarisations. HRV is the measurement of the variability of the N–N intervals and is regarded as an indicator of the activity of autonomic regulation of circulatory function.

Various measures of HRV have been proposed. These can be divided into time domain, frequency domain and non-linear measures. A simple example of a time domain measure is the standard deviation of beat-to-beat intervals. Other time domain measures include the root mean square of the differences between heart beats (NN RMSSD) and NN 50, the number of instances in which two consecutive intervals differ by more than 50 ms.

It has been shown that patients with underlying cardiovascular conditions such as previous myocardial infarction and congestive cardiac failure

have reduced HRV.[15 16] HRV falls within 2 to 3 days after a myocardial infarction, begins to recover within a few weeks and is maximally but not fully recovered by 6–12 months.[15] Patients with persistently low HRV have mortality almost three times greater than those with normal HRV.[17]

Equally, autonomic imbalance is thought to play an important role in the pathogenesis of neurally mediated syncope, with patients who have cardioinhibitory or vasodepressive findings on tilt table testing showing markedly increased HRV. Salemeh *et al*[18] demonstrated increased HRV time domain parameters in the 24-h ambulatory ECG in 123 patients who had positive tilt table testing compared with 83 healthy volunteers. Arslan *et al*[19] demonstrated higher time domain HRV parameters in 24-h recordings of 17 patients who had a positive tilt table test compared with 16 control patients. It is thought that patients who have neurocardiogenic syncope have a greater baseline HRV compared with controls, who again have greater HRV than patients with underlying cardiac disease.

The aim of this study was to assess the feasibility of using the technique of HRV to predict risk in patients presenting to the ED with syncope. The secondary aim was to determine whether HRV characteristics may be useful to distinguish low-risk syncope patients (likely to have had an episode of neurocardiogenic syncope or postural hypotension) from high-risk patients who are more likely to have had a life-threatening arrhythmia and control patients without syncope.

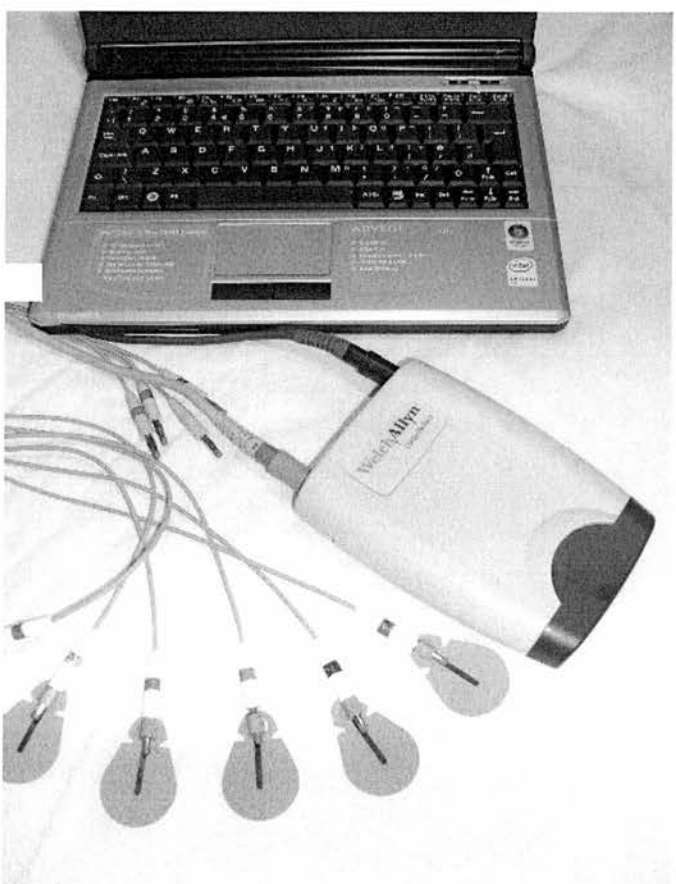

Figure 1 Photograph of the WelchAllyn Cardioperfect electrocardiogram 12-lead ECG recorder box.

METHODS

The study was undertaken in the ED of the Royal Infirmary of Edinburgh (a tertiary centre seeing 95 000 adult attendances per annum) in July 2007. A convenience sample of all patients aged 16 years or over who presented to the ED with syncope when the study researcher (MEB) was present, was recruited. The study researcher worked in the ED on weekdays between 10:00 and 18:00 hours and was based in the clinical area to ensure that all eligible patients were recruited. Syncope was defined as a transient loss of consciousness with an inability to maintain postural tone followed by a spontaneous recovery without the need for therapeutic or electrical intervention. Patients under 16 years of age, those previously recruited and those having a history of seizure with a prolonged postictal phase were excluded. Patients who were unable to give either written or verbal informed consent were also excluded.

Eligible patients were identified by the study researcher on arrival at the ED. A 5-minute 12-lead ECG tracing was performed at the bedside by the study researcher (MEB) using the WelchAllyn Cardioperfect electrocardiogram system, which was supplied by WelchAllyn for the duration of the study. The Cardioperfect 12-lead ECG recorder box is a pocket-sized device with attached leads that can be powered either by battery or directly through a USB connection to a portable laptop (fig 1). The data can then be downloaded and interpreted using the software supplied.

A second researcher (MJR), blinded to the HRV results, independently scrutinised the ED notes of all recruited patients and divided patients into high, medium or low-risk categories according to the ED's existing syncope guidelines (see appendix). This researcher also independently divided patients into one of four likely diagnostic categories: vasovagal; postural hypotension; possible cardiac and other. Patients with a recorded postural drop of 20 mm Hg or greater with no obvious other cause (ie, ruptured abdominal aortic aneurysm) were categorised with postural hypotension. Patients with symptoms of nausea, diaphoresis, dizziness and a feeling of warmth before collapse were designated as vasovagal; patients with a brief or absent presyncopal period or cardiac abnormalities on examination were classified as possible cardiac syncope and finally

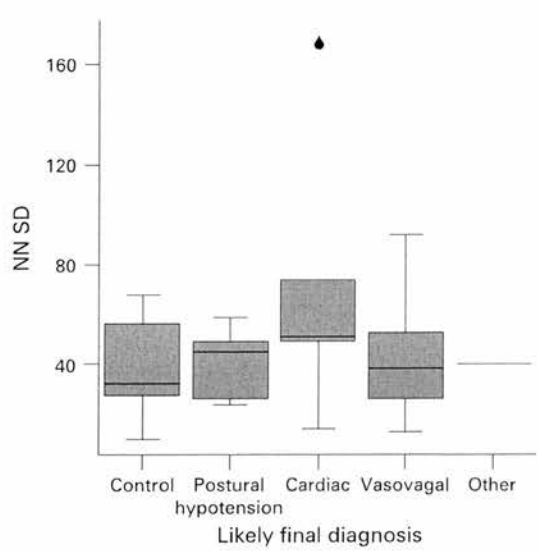

Figure 2 Box plot showing NN SD according to likely final diagnosis (one patient had "other" diagnosis).

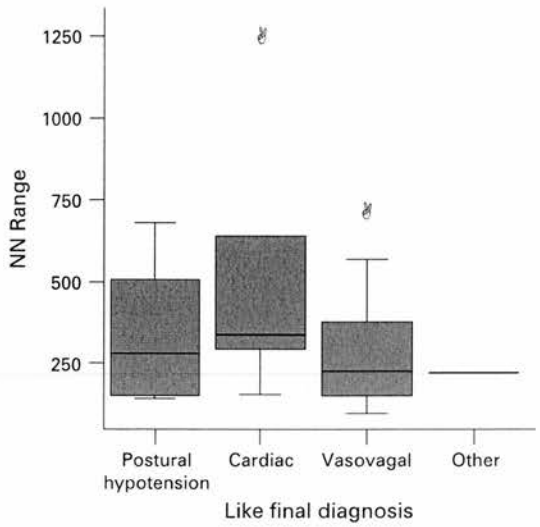

Figure 3 Box plot showing NN range according to likely final diagnosis (one patient had "other" diagnosis).

patients with an obvious other cause, ie, cough/micturition/glyceryl trinitrate syncope were defined as "other".

The 5-minute ECG signals from all patients were then analysed using the WelchAllyn Cardioperfect ECG interpretation software (Cardioperfect 1.5.0.434) provided. ECG traces that were not in sinus rhythm (ie, atrial fibrillation) and those that did not display the usual P, QRS and T wave configuration (ie, left bundle branch block and right bundle branch block) were not suitable for analysis and were discarded. The Cardioperfect software was then used to calculate time domain HRV parameters. Those considered were the number of normal R–R intervals (NN number), the maximum, minimum, range and mean normal R–R intervals (NN minimum, NN maximum, NN range and NN mean), the standard deviation of normal R–R intervals (NN SD), the standard deviation of the averages of normal R–R intervals (NN avgdev), the NN RMSSD (root mean square successive differences) and the number of instances in which two consecutive R–R intervals differed by more than 50 ms (NN 50). A non-matched control group of ED staff volunteers without previous cardiovascular or syncopal illness was also recruited. The purpose of this control group was to elucidate any differences in HRV characteristics between each diagnostic group and an apparently healthy population. This group also had a 5-minute 12-lead ECG tracing performed and analysed according to the same protocol as the study patients.

No previous sample size calculation was performed as this was an explanatory pilot study. All data were analysed using SPSS. Normal distribution was assumed for all variables and mean values and confidence intervals were calculated for age, heart rate, QRS axis and duration and HRV parameters. Because of the small sample size, confidence intervals were conservatively calculated using interval estimates based on the t distribution and differences between groups were analysed using descriptive inference. Hypothesis tests were not performed due to the large quantity of data collected and the small number of patients.

This study received full ethical approval from the MREC for Scotland A Ethics Committee (reference: 06/MRE00/107—substantial amendment no 2) and Lothian REC (reference: 06/S11ADMIN/151) on 14 May 2007. Lothian R&D management approval was also obtained.

RESULTS

A total of 32 patients and 23 controls was recruited. The ECG tracings of five patients in the study group were not suitable for analysis and were discarded, leaving 27 patients suitable for subsequent analysis. Of these patients, five were thought to have had an episode of postural hypotension, 16 patients a vasovagal and five a possible cardiac arrhythmia or other cardiopulmonary cause for their syncopal episode (table 1). Only one patient, who had cough syncope, received a diagnosis of "other". No data are therefore reported for this category. Vasovagal patients were younger than patients with postural hypotension. Patients with cardiac syncope had greater mean values for all HRV characteristics except NN number and NN minimum (fig 2 and fig 3), however, with overlapping confidence intervals. Nine patients were thought to be low risk, 12 medium risk and six high risk according to our existing ED syncope guidelines (table 2). Low-risk patients were more likely to be younger than medium and high-risk patients. No HRV parameters showed any significant differences.

Table 1 HRV characteristics according to final likely diagnosis

	Control (n = 23)		Postural hypotension (n = 5)		Cardiac (n = 5)		Vasovagal (n = 16)	
	Mean	CI	Mean	CI	Mean	CI	Mean	CI
Age, years	42	37 to 47	79	75 to 82	71	51 to 91	55	46 to 64
Heart rate	73	68 to 79	80	52 to 109	67	53 to 80	69	61 to 78
QRS axis	37	17 to 57	2	−24 to 28	8	−37 to 54	32	12 to 53
QRS duration	92	87 to 97	98	84 to 112	104	59 to 149	92	87 to 97
QTc	410	403 to 417	422	409 to 436	417	391 to 443	423	413 to 432
NN number	365	339 to 391	402	257 to 546	328	266 to 390	344	302 to 387
NN minimum	714	670 to 757	573	395 to 752	727	465 to 990	756	665 to 847
NN maximum	980	904 to 1055	941	639 to 1242	1270	863 to 1677	1041	944 to 1138
NN range	264	204 to 323	353	61 to 644	543	−16 to 1101	285	184 to 385
NN mean	838	785 to 891	788	546 to 1030	930	742 to 1118	902	814 to 989
NN SD	40	32 to 47	41	22 to 59	72	−2 to 146	43	30 to 55
NN avgdev	31	25 to 38	25	16 to 33	54	1 to 107	33	22 to 43
NN RMSSD	32	24 to 40	47	3 to 91	76	−38 to 191	33	18 to 48
NN 50	42	18 to 65	48	−67 to 163	85	−64 to 233	32	1 to 62

CI, confidence intervals; HRV, heart rate variability; NN avgdev, standard deviation of the averages of normal R–R intervals; NN RMSSD, root mean square of the differences between heart beats; NN 50, the number of instances in which two consecutive intervals differ by more than 50 ms.

Table 2 HRV characteristics according to ED guideline risk

	Control (n = 23)		Low risk (n = 9)		Medium risk (n = 12)		High risk (n = 6)	
	Mean	CI	Mean	CI	Mean	CI	Mean	CI
Age, years	42	37 to 47	41	31 to 51	72	65 to 78	70	55 to 86
Heart rate	73	68 to 79	68	61 to 75	72	60 to 83	76	51 to 101
QRS axis	37	17 to 57	35	10 to 60	7	−60 to 74	38	19 to 57
QRS duration	92	87 to 97	89	82 to 96	95	89 to 102	103	69 to 137
QTc	410	403 to 417	415	400 to 430	423	411 to 434	425	412 to 437
NN number	365	339 to 391	337	305 to 370	356	299 to 412	377	251 to 504
NN minimum	714	670 to 757	776	694 to 857	663	544 to 782	720	468 to 972
NN maximum	980	904 to 1055	1032	924 to 1139	1102	916 to 1287	1012	729 to 1294
NN range	263	204 to 323	256	153 to 359	433	211 to 655	292	103 to 481
NN mean	838	785 to 891	899	809 to 989	879	768 to 990	854	606 to 1101
NN SD	40	32 to 47	50	30 to 70	48	21 to 75	42	28 to 56
NN avgdev	31	25 to 38	41	24 to 57	33	13 to 53	30	22 to 39
NN RMSSD	32	24 to 40	38	15 to 61	52	11 to 92	36	4 to 68
NN 50	42	18 to 65	55	2 to 108	39	−13 to 92	42	−46 to 130

CI, confidence intervals; ED, emergency department; HRV, heart rate variability; NN avgdev, standard deviation of the averages of normal R–R intervals; NN RMSSD, root mean square of the differences between heart beats; NN 50, the number of instances in which two consecutive intervals differ by more than 50 ms.

DISCUSSION

Our results suggest that although there seems to be no significant difference between HRV values and syncope risk groups, patients with a possible diagnosis of cardiac syncope had a trend towards greater mean values for most HRV characteristics. Although there is some disagreement between studies, our results seem to contrast with previous studies, which have suggested that patients who have neurocardiogenic syncope have a greater baseline HRV compared with controls, who again have greater HRV than patients with underlying cardiac disease. There may be several reasons for this discrepancy. First, the study enrolled a relatively small number of patients and there were few serious outcomes or deaths. There was also no formal protocol in place to identify patients' final diagnosis. Rather, the determination of risk and likely underlying diagnosis was done by the researchers looking through study patients' ED notes and hospital records. This may have introduced a subjective element to the determination of risk and likely underlying diagnosis. If a further large study were to be undertaken, an investigation protocol would be required in order to determine as accurately as possible each patient's underlying syncope diagnosis. Other endpoints such as death or serious outcome would also need to be considered. Because of its explanatory nature, a sample size was not determined before commencing this study. This would be required before a further large study.

Most HRV studies are not performed in the acute situation. Patients tend to be recruited from those who have chronic neurocardiogenic syncope, or from those who have a history of cardiac disease and then HRV analysis is performed at some time distant from their index or most recent event. There are very few studies that have looked at syncope patients' HRV characteristics in the acute setting.

This pilot study has shown that the technique of HRV can be performed on patients presenting acutely to the ED with syncope. Although this study did not reveal any previously reported differences between high-risk syncope patients who may go on to develop life-threatening arrhythmias and low-risk patients with postural hypotension or neurocardiogenic syncope, it has provided useful data to demonstrate the feasibility of HRV measurement in the ED and has allowed a more definitive study to be planned.

CONCLUSIONS

This study has demonstrated that it is feasible to measure HRV in the acute setting in patients presenting with syncope to the ED. Although the study did not demonstrate any significant differences in HRV parameters between patients with likely different causes for their syncope, the technique is feasible and simple to perform within the ED and a larger study may be warranted.

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APPENDIX

Royal Infirmary of Edinburgh Emergency Department existing syncope guidelines based on the European Society of Cardiology,[5 6] American College of Physicians[2 3] and American College of Emergency Physicians[4] guidelines

High risk (admit)

History findings

- Palpitations related to syncope
- Associated chest pain
- Associated headache
- Related to exertion
- Family history of sudden death <60 years
- Previous history of ventricular tachycardia/ventricular fibrillation/cardiac arrest

Examination findings

- Systolic heart murmur heard
- Signs of heart failure present
- Systolic blood pressure <90 mm Hg
- Suspicion of pulmonary embolism
- Abdominal aortic aneurysm detected
- New neurological signs on examination
- Suspicion of cerebrovascular accident or subarachnoid haemorrhage
- Faecal occult blood present on per recturn examination
- Other suspicions of gastrointestinal bleed

ECG findings

- Mobitz type II heart block
- Wenkebachs type II heart block
- Bifascicular block
- Complete heart block
- Sinus pause >3 s
- NEW ST elevation
- Ventricular tachycardia
- Sinus bradycardia <50
- Sino-atrial block
- QTc >450 ms
- NEW T wave/ST segment changes
- Brugadas (ST segment elevation V1–V3)
- Arrhythmogenic right ventricular dysplasia

Medium risk (consider discharge with early outpatient review)

History findings

- Age >60 years
- No prodromal symptoms
- Previous myocardial infarct
- Known history of valvular heart disease
- Known angina/coronary artery disease
- Known history of congestive cardiac failure

Examination findings

- >20 mm Hg drop on standing
- Diastolic heart murmur heard
- Ventricular pause >3 s on carotid sinus massage
- Trauma associated with collapse

ECG findings

- Right bundle branch block
- QRS duration >120 ms
- OLD T wave/ST segment changes
- Frequent pre-excited QRC complexes
- Q-waves unchanged from old ECG
- Atrial fibrillation or flutter
- Pulse rate >200 ms (first-degree heart block)

Low risk (consider discharge)

- None of the above characteristics

Syncope management in the UK and Republic of Ireland

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► The appendix is published online only at http://emj.bmj.com/content/vol26/issue5

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ABSTRACT

Aims: To establish the current practice of emergency department (ED) management of syncope in the UK and Republic of Ireland.

Methods: A survey of "major" or "intermediate" size ED in the UK and Republic of Ireland conducted by postal and telephone questionnaire.

Results: 177 (70%) ED responded. 32 (18%) ED have syncope guidelines, which are based on a range of existing guidelines. 97 ED (55%) have an observation ward or clinical decision unit and 48 (49%) of these admit syncope patients to these units. 32 ED (18%) have access to a specialist syncope outpatient clinic. This is most likely to be run by general practitioner specialists (43%) or general physicians (24%). 81% of ED felt that improved research-based guidelines would be useful when managing syncope patients.

Conclusion: The ED management of syncope patients in the UK and Republic of Ireland is varied. Only 18% of ED have specific guidelines for managing this difficult condition and only 18% have access to a specialist syncope clinic. A robust consensus UK syncope guideline is clearly required.

Syncope is a sudden but brief loss of consciousness with an inability to maintain postural tone followed by a spontaneous recovery. It is a common presentation to the emergency department (ED), accounting for between 1% and 2% of all visits each year.[1] As the causes of syncope range from the benign to the life threatening, it is important to establish the risk to the patient as effectively as possible. Several guidelines and risk stratification tools exist aiming to identify high-risk patients requiring further investigation accurately and low-risk patients who may be discharged safely.[2–12] None of these tools have been derived from or validated in a UK or Republic of Ireland population. In the USA, where many of these tools and guidelines were developed, consensus with regard to a universal approach to patients remains lacking.[13]

The aims of this study were to establish the current practice of ED management of syncope in the UK and Republic of Ireland, to investigate whether improved research-based guidelines are required and to evaluate what facilities are available in UK ED to which such guidelines could be tailored.

METHODS

A questionnaire and accompanying letter was designed by the study authors (see the appendix available online only). An electronic list of all 312 ED in the UK and Republic of Ireland was obtained from the British Association for Accident and Emergency Medicine (BAEM) in September 2007. ED not listed as "major" or "intermediate" in the last BAEM directory were removed, leaving 254 ED. The questionnaire with a covering letter and a pre-paid return envelope was then sent out to a named consultant at each one of the 254 ED. After a month the questionnaire was resent to those ED that had not initially responded (157) this time addressed to "Nurse in charge". Finally those ED that had not responded after two attempts (86) were telephoned (fig 1). This study was designed in accordance with published recommended guidelines for ED questionnaires.[14 15]

RESULTS

A total of 177 ED (70%) responded; 32 (18%) have syncope guidelines. Of these, six are based on the European Society of Cardiology guidelines,[8 9] four on the American College of Emergency Physicians guidelines,[12] six on the American College of Physicians guidelines,[10 11] two on the OESIL syncope score,[6] three on the San Francisco syncope rule[4 5] and eight on "other", usually an ED consultant personal opinion. Nine gave no response to this question and four guidelines are based on more than one source. Of the 32 ED with guidelines, 22 are in paper form, three are in poster format and 12 are in electronic form.

Of the 32 ED with syncope guidelines, 22 are for ED use only and six are general hospital guidelines. Table 1 shows the comparison of ED with and without syncope guidelines; 97 of 177 ED (55%) have an observation ward or clinical decision unit; 48 (49%) of these admit syncope patients to the unit. Thirty-two ED (18%) have access to a specialist syncope outpatient clinic; 28 of these 32 ED (88%) can access this clinic from the ED. Figure 2 displays which specialty runs this clinic. Seventy-eight ED (44%) have access to near-patient testing in their ED and eight (5%) use near-patient brain natriuretic peptide testing in their ED.

DISCUSSION

This is the first survey to describe the management of syncope in UK emergency medical practice. It clearly shows marked variation in routine practice in the UK and Republic of Ireland. We managed to achieve a 70% response rate to our questionnaire. This compares favourably with similar studies. There is no reason to suspect that these results are not generalisable to all medium and large size UK ED. It is of interest how few ED have syncope guidelines to assist decision-making given the complexity of risk stratification and disposition of this common ED presentation. Eighty-one per

Table 1 Comparison of ED with and without syncope guidelines

	ED with syncope guidelines (n = 32)	ED without syncope guidelines (n = 145)
Does your hospital have single or separate front doors for medical/GP referral/ED patients?	16 single (50%)	57 single (39%)
	3 no response (9%)	7 no response (5%)
	13 separate (41%)	81 separate (56%)
Does your ED have an observation ward/clinical decision unit?	18 yes (56%)	79 yes (54%)
	14 no (44%)	3 no response (2%)
		63 no (43%)
Does your hospital have a specialist syncope outpatient clinic?	10 yes (31%)	22 yes (15%)
	1 no reply (3%)	5 no reply (3%)
	21 no (66%)	118 no (82%)
Do you think more research-based guidelines would be useful when managing patients presenting with syncope to the ED?	24 yes (75%)	120 yes (83%)
	3 no reply (9%)	6 no reply (4%)
	5 no (16%)	19 no (13%)
Do you have access to near-patient testing in your ED?	14 yes (44%)	64 yes (44%)
	2 no response (6%)	78 no (54%)
	16 no (50%)	3 no reply (2%)

ED, emergency department; GP, general practitioner.

cent of ED felt that improved research-based guidelines would be of use when managing syncope patients. Although we did not specifically ask why guidelines were not used, these findings may suggest dissatisfaction with existing guidelines. It is our belief that the lack of a UK ED orientated guideline has led some ED to construct their own guidelines based on a variety of sources, whereas others simply have no advice in place. A consensus UK guideline similar to that published by the American College of Emergency Physicians is clearly required.

Eighteen per cent of ED have access to a specialised syncope clinic. This is more common in ED with existing guidelines. It is likely that in these ED, the clinic forms part of a structured pathway of care with the identification of low-risk patients safe to be discharged and medium-risk patients who may be able to go home with early follow-up and investigation. Many ED have an observation ward or clinical decision unit and many already admit syncope patients to this. There is clearly scope to manage syncopal patients in a similar way to other common conditions such as chest pain with a period of observation, along with risk stratification in the form of echocardiography and biochemical markers. Forty-four per cent of ED already use near-patient testing and 5% have access to near-patient brain natriuretic peptide, a biomarker currently undergoing investigation as a syncope biomarker.[16]

We suggest that once completed, the results from the ROSE study, the first UK emergency medicine specific clinical decision rule for the management of syncope, could be used to form the basis of a College of Emergency Medicine approved UK syncope guideline. We envisage that this guideline would utilise existing pathways sent to us from other services in the UK and Republic of Ireland. If the ROSE study safely identifies low-risk patients then a robust consensus guideline may also support the immediate discharge of certain patient groups who could receive further evaluation in specialist syncope outpatient clinics.

CONCLUSION

The ED management of syncope patients in the UK and Republic of Ireland is varied. Only 18% of ED have specific

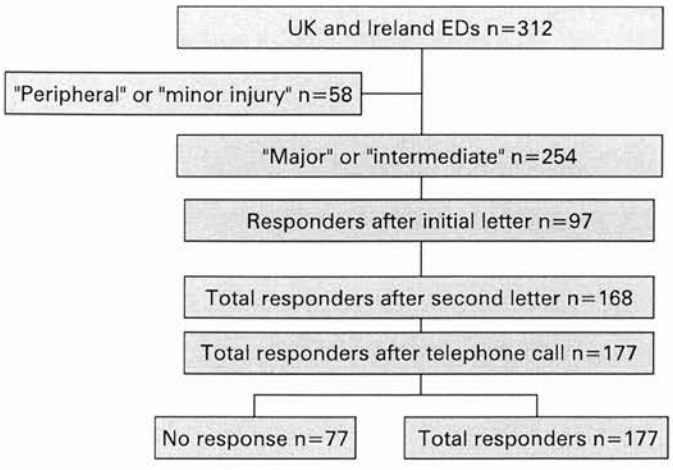

Figure 1 CONSORT type diagram of study enrolment. ED, emergency department.

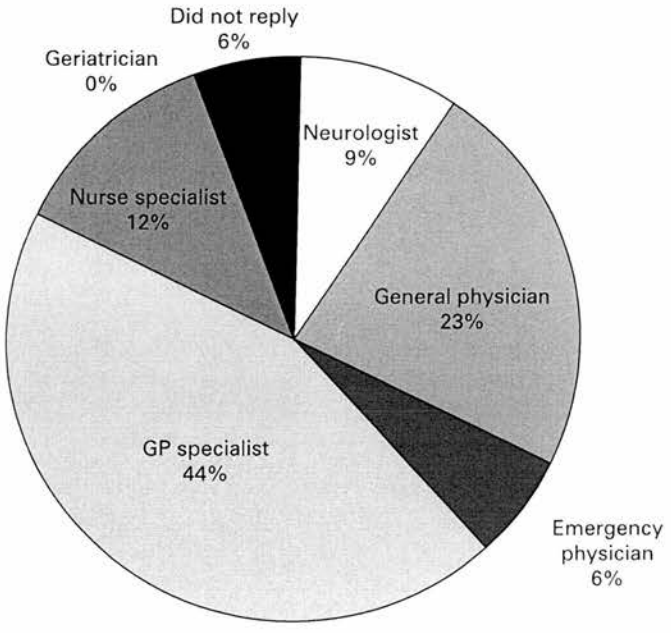

Figure 2 Pie chart demonstrating personnel running syncope outpatient clinic. GP, general practitioner.

guidelines for managing this difficult and common condition and only 18% have access to a specialist syncope clinic.

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Competing interests: None.

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